POLYMER SUPPORTED AND HOMOGENEOUS ORGANOCATALYSTS FOR ASYMMETRIC REACTIONS: FROM BATCH TO CONTINUOUS FLOW APPLICATIONS

PhD Thesis

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Prof. MIQUEL A. PERICÀS, Group Leader of Research Group and Director of the Institute of Chemical Research of Catalonia (ICIQ),

CERTIFIES, that the present Doctoral Thesis entitled "**POLYMER SUPPORTED AND HOMOGENEOUS ORGANOCATALYSTS FOR ASYMMETRIC REACTIONS: FROM BATCH TO CONTINUOUS FLOW APPLICATIONS**" presented by **Pinar KASAPLAR OZKAL** to obtain the degree of Doctor, has been carried out under my supervision in the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, January 14, 2014

PhD Thesis supervisor

Prof. Miquel A. Pericàs

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Tarragona, March 2014

To my family

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List of Publications

The PhD Thesis is based on the following publications:

- "*Polystyrene-Supported Diarylprolinol Ethers as Highly Efficient Organocatalysts for Michael-Type reactions*" Esther Alza, Sonia Sayalero, Pinar Kasaplar, Diana Almasi, and Miquel A. Pericàs. *Chem. Eur. J.* **2011**, *17*, 11585-11595.

- "*A Polystyrene-Supported, Highly Recyclable Squaramide Organocatalyst for the Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to β-Nitrostyrenes*" Pinar Kasaplar, Paola Riente, Caroline Hartmann, and Miquel A. Pericàs. *Adv. Synth. Catal.* **2012**, *354*, 2905-2910.

- "*Continuous Flow, Highly Enantioselective Michael Additions Catalyzed by a PS-Supported Squaramide*" Pinar Kasaplar, Carles Rodríguez-Escrich, and Miquel A. Pericàs. *Org. Lett.* **2013**, *15*, 3498-3501.

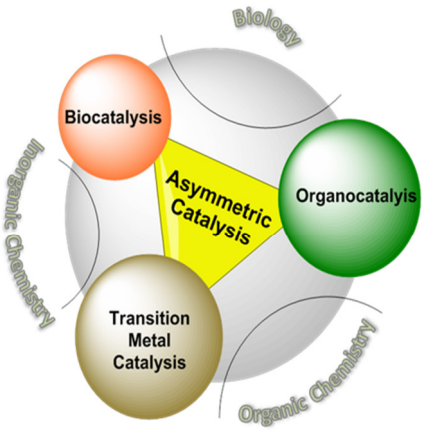
Acronyms and Abbreviations

In this document the abbreviations and acronyms most commonly used in organic chemistry have been used, according to the recommendations of the ACS "*Guidelines for authors*" *J. Org. Chem.* **2008**, *73*, 23A-24A.

http://pubs.acs.org/paragonplus/submission/joceah/joceah_authguide.pdf

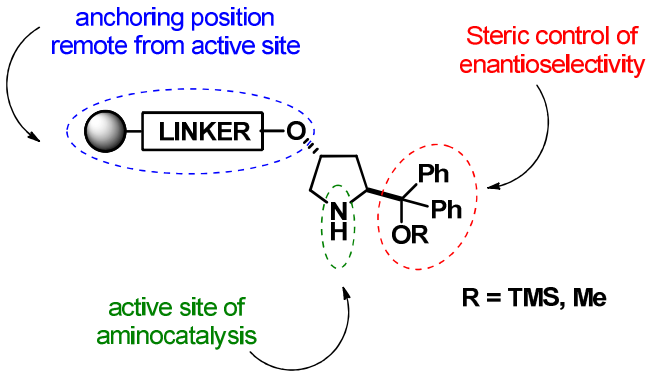
GRAPHICAL ABSTRACTS

CHAPTER I – General Introduction (1-30)



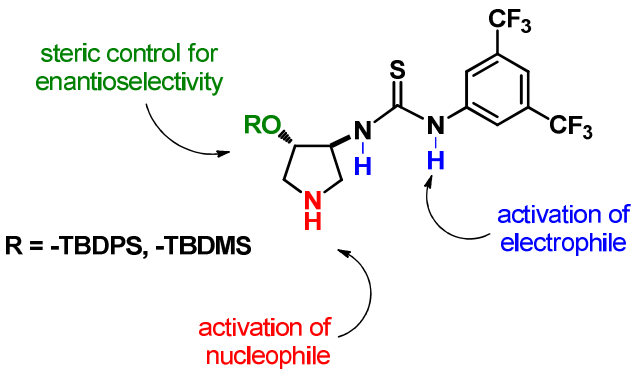
The purpose of this chapter is to familiarize the reader to the concepts behind in this thesis. The general aim of this thesis is to establish a synthetic route for the immobilization of organocatalysts to polymer support. General concerns of organocatalysts and solid supports, which are the main focus of this thesis, are described. Finally, the objectives of the thesis have been defined.

CHAPTER II – PAPER A (31-78)



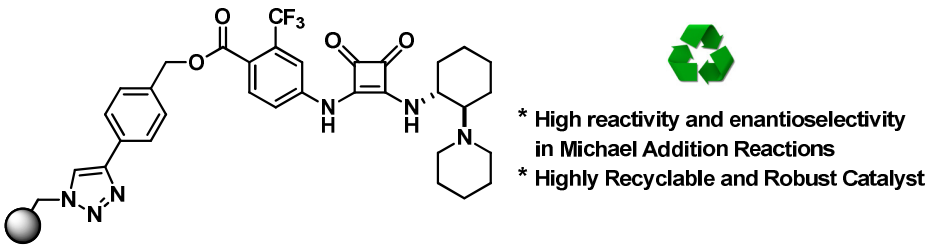
The synthesis of polystyrene (PS) supported α,α-Diphenylprolinol methyl- and trimethylsilyl ethers via copper-catalyzed azide–alkyne cycloadditions (CuAAC) have been described. The catalytic activity and enantioselectivity for the addition of aldehydes to nitroolefins and malonates or nitromethane to α,β-unsaturated aldehydes were evaluated. Reactions are preceded via an enamine and iminium ion intermediates successfully. The catalytic behavior of polystyrene-supported α,α-diphenylprolinol methyl ether was also evaluated in asymmetric Michael addition reactions however moderate performance was observed relative to O-trimethylsilyl derivative (Paper A).

CHAPTER III – PYRROLIDINE-BASED THIOUREA ORGANOCATALYST (79-108)



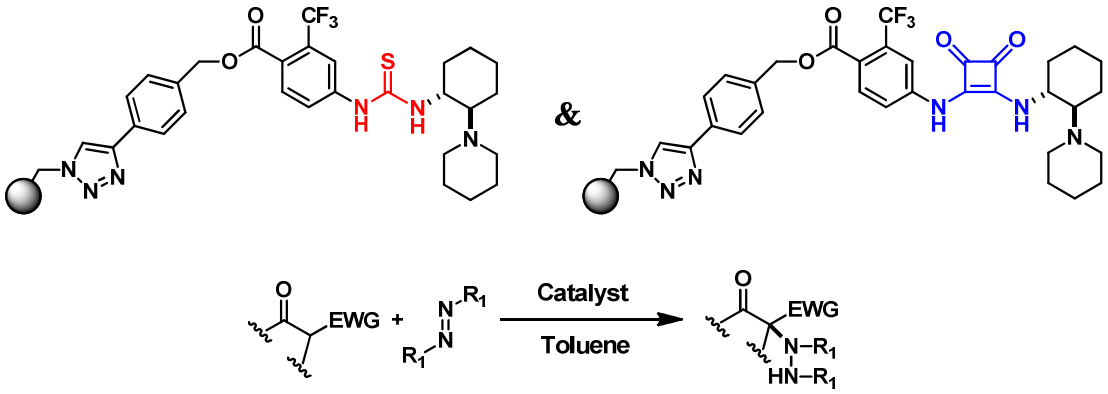
The pyrrolidine-based thiourea organocatalyst obtained via desymmetrization of meso-*N*-trifluoroacetyl-3-pyrroline oxide which allowed us for the functionalization of pyrrolidine ring from C3 and C4 positions. The synthesized bifunctional catalysts have a hydrogen bond donating group and a pyrrolidine ring for the activation of both electrophiles and nucleophiles. The designed catalyst activities were evaluated in the enantioselective *anti*-Mannich reactions.

CHAPTER IV-I – PAPER B and C (109-202)



The design and synthesis of polystyrene-supported squaramide organocatalyst and its evaluation in the Michael addition of 1,3-dicarbonyl compounds to β-nitrostyrenes have been described (Paper B). The same catalyst has been used in the Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes with very high enantioselectivities at low catalyst loadings. This PS-supported squaramide organocatalyst has also been demonstrated as a highly reactive and robust catalyst for continuous flow application (Paper C).

CHAPTER IV-II – PS-SUPPORTED THOIUREA & SQUARAMIDE ORGANOCATALYSTS (203-226)



The PS-supported thiourea organocatalyst was prepared with an approach adapted from the synthesis of squaramide organocatalyst. Both of these polystyrene supported catalysts were used in the α-amination reaction and good to moderate results were obtained. An alternative approaches were described for the synthesis of PS-supported thiourea organocatalysts.

CONCLUSIONS & OUTLOOK (227-232)

CHAPTER I

1. GENERAL INTRODUCTION

The concept of chemical catalysis is now more than a century old. From the beginning, several definitions were used for the word *catalyst*. In 1912, Paul Sabatier (Nobel laureate in Chemistry in 1912) defined catalysts as "*compounds involved in chemical reactions to generate or accelerate the reaction without being product of the reaction"*. Since then, catalysis has grown to be a very important research area that can be classified under three headings: homogeneous, heterogeneous and enzymatic catalysis.[1]

Over the years, this classification has been extended and the field of asymmetric catalysis has gained importance to become a crucial topic in organic synthesis. Before going into details of the importance of asymmetric catalysis, it is essential to define the term chirality. Chirality is a property related with the geometry of the molecules, the term was first introduced into science by Lord Kelvin (William Thomson), Professor of Natural Philosophy in the University of Glasgow (1846-1899): "*I call any geometrical figure, or group of points, chiral, and say that it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself*."[2] According to this primary definition, two molecules that are mirror images of each other but non-superimposable are called enantiomers. Chirality is a vital property of the molecules of life, defining reactivity, substrate binding, and recognition; nearly all molecules in nature have a so called "left or right hand" form, such as amino acids, enzymes, alkaloids, terpenes, etc. This unique one-handedness feature is essential for the biological and pharmaceutical activity of many molecules. Indeed, two enantiomers of the same molecule will have the same physical properties, but their biological activity can be very different. For this reason, chemists in academia and industry, especially in pharmacy, devote great effort to the synthesis of enantiomerically pure compounds.

Awareness of the side effects of achiral compounds in drug action has increased the importance of chiral molecules in pharmacology. For instance, a very classical example, one form of thalidomide lessens morning sickness; on the

[1] Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis Vols I–III*, *Springer*, *Heidelberg*, **1999**.
[2] Kelvin, W. T. *The second Robert Boyer lecture, J. Oxford Univ. Junior Sci. Club* **1884**, *18*, 25.

other hand, the other form may cause birth defects.[3] There are several other examples like this drug: while one enantiomer shows beneficial reactivity on disease, the other may have toxicity. Consequently, using the correct form of a chiral molecule is a must to be able to categorize it as an approved drug. Thus, the synthesis of chiral molecule has an upmost importance in general.

The synthesis of chiral compounds can be achieved by the resolution of racemates, via asymmetric synthesis (chemically or enzymatically) or through chiral starting materials. The first catalytic asymmetric reaction from racemic compounds via kinetic resolution was done by Pasteur in 1858 and the first enzyme-mediated catalytic asymmetric reaction was used in the synthesis of mandelonitrile in the addition of hydrogen cyanide to benzaldehyde by Rosenthaler in 1908.[1] Furthermore, asymmetric catalysts[4] play a significant role in the synthesis of chiral molecules. The most prominent development in asymmetric catalysis occurred in the 1970's. Knowles *et al.* showed that rhodium complexes containing chiral phosphine ligands ([Rh(*R,R*)-DiPAMP)COD]BF_4) were able to catalyze the asymmetric hydrogenation of olefinic substrates generating a chiral center with high enantioselectivity.[4,5] They commercialized this asymmetric hydrogenation process for the synthesis of L-DOPA (L-3,4-dihydroxy-phenylalanine), which is used in the treatment of Parkinson disease. Knowles was awarded the Nobel Prize in chemistry in 2001 (together with Ryoji Noyori and K. Barry Sharpless) for his work on the asymmetric catalytic hydrogenation.

Nowadays, asymmetric catalysis plays a pivotal role in the synthesis of enantiomerically pure compounds. This concept includes biocatalysis, organometallic catalysis and organocatalysis (Figure 1.1). The focus of the present thesis has been made in organocatalysis, so the general introduction will continue along this direction.

[3] Brynner, R.; Stephens, T.; *Dark Remedy: the Impact of Thalidomide and its Revival as a Vital Medicine, Perseus Publishing*, *Cambridge MA*, **2001**.
[4] Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, *Wiley*, *New York*, **1994**.
[5] Knowles, W. *Acc. Chem. Res*. **1983**, *16*, 106-112.

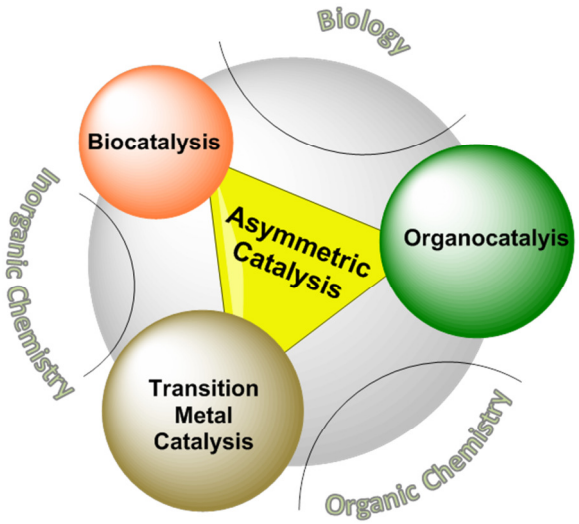


Figure 1.1. Asymmetric Catalysis.

1.1. ORGANOCATALYSIS

The term *organocatalysis* refers to the use of substoichiometric amounts of small molecules, which contain mainly C, H, N, O, S, and P elements, to accelerate chemical reactions.[6] Since its conceptualization in the year 2000, organocatalysis has become one of the hot topics in organic chemistry, attracting the interest of the chemical community. Their main advantages include ease of handling, low toxicity, and relatively low price with respect to precious metals and in most cases air and moisture insensitivity which makes them interesting catalysts even for industry.

Organocatalysis can be divided in two main categories according to the character of substrate and catalyst-substrate interactions: “covalent” and “non-covalent” catalysis (Figure 1.2).[7] In addition, organocatalysts have been classified according to their nature of activation by List as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids.[8] (Scheme 1.1) Although these classifications have some limitations and could be enlarged to several headings, in this thesis we will describe reactions according to the general mode of activation and to the chemical nature of the catalysts.

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[6] Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138-5175.
[7] Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: from Biomimetic Concepts to Applications in Asymmetric Synthesis, Wiley VCH*, *Weinheim*, **2005**. b) Moyano, A.; and Rios, R. *Chem. Rev.* **2011**, *111*, 4703-4832.
[8] Seayad, J.; List, B. *Org. Biomol. Chem*. **2005**, *3*, 719-724.

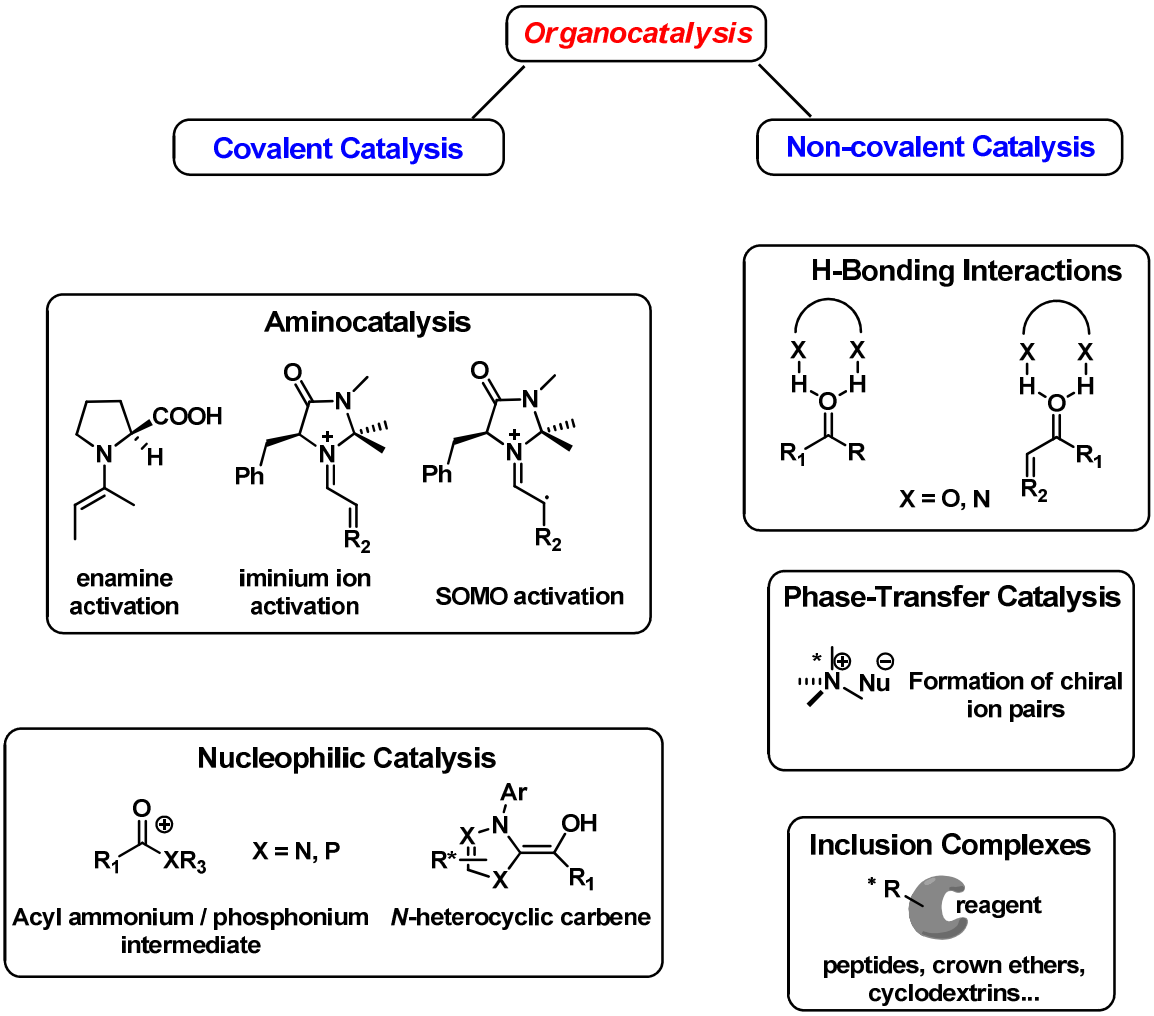
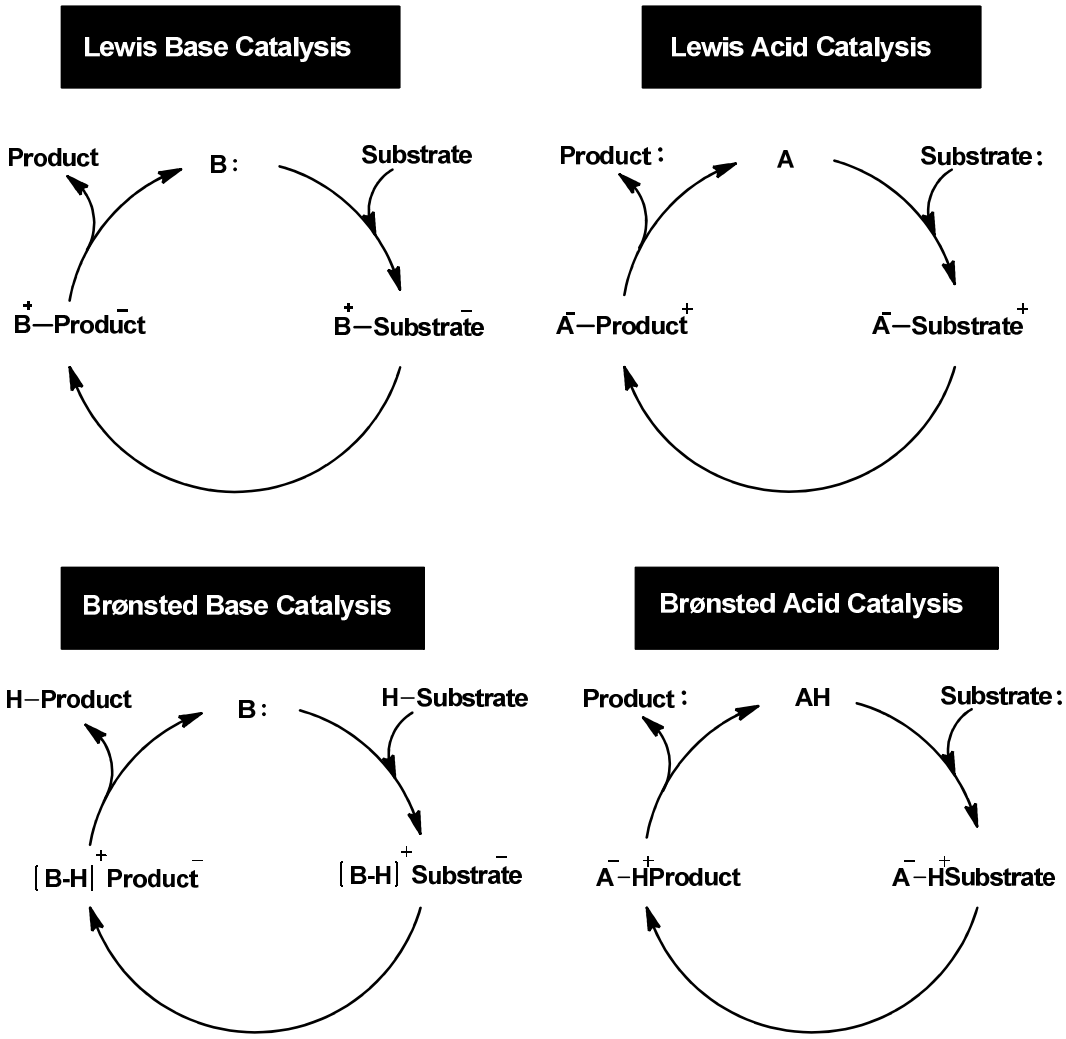


Figure 1.2. Organocatalysis classification as covalent and non-covalent catalysis.

1.1.1. Lewis Base Catalysis

Aminocatalytic activation modes namely enamine, iminium and SOMO activation are, first of all, classified as covalent catalysis in terms of catalyst-substrate interaction, and then, as Lewis base catalysis due to their reactivity pattern. A Lewis base catalyst participates in reactions activating the substrate by means of nucleophilic addition or substitution.[9] As depicted in (Scheme 1.1), a general mechanism for Lewis base catalysis is initiated by nucleophilic addition to the substrate to form an activated nucleophilic or electrophilic species. After the bond forming event triggered by these reactive intermediates, the product is formed and the catalyst is released, ready to participate in another cycle.

[9] Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E.; *Organocatalytic Enantioselective Conjugate Addition Reactions, RCS Publishing, Cambridge*, **2010**.



Scheme 1.1. Organocatalytic cycles

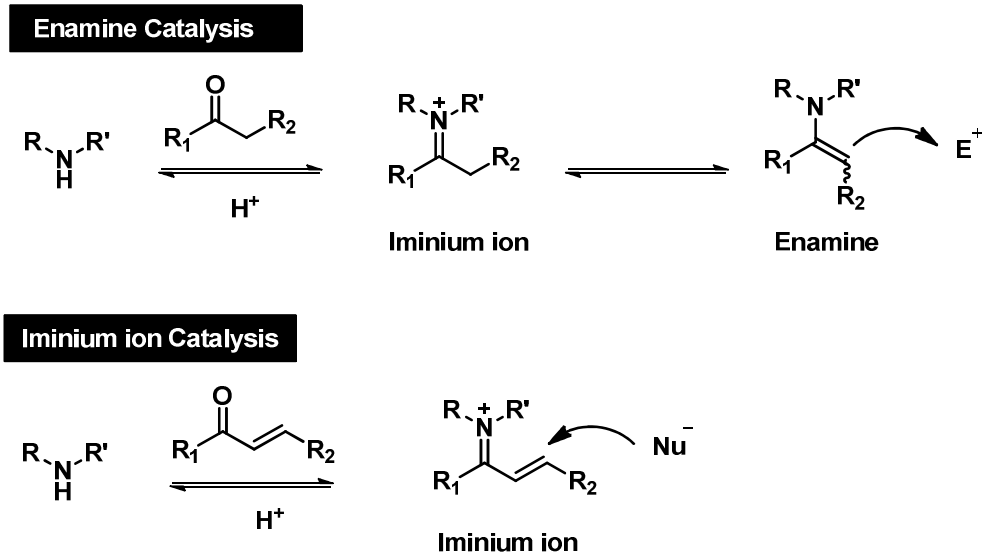
Enamine catalysis grew quickly to become one of the privileged activation modes of the golden age of organocatalysis. An enamine is generated from the condensation of a chiral amine and a carbonyl compound and this intermediate is nucleophilic in the α-position (Scheme 1.2).[10] Enamines are able to react with a large number of electrophiles and this feature makes them a versatile activation mode for several transformations.

Although the first aminocatalyst was used in the 1970's by Hajos, Parrish, Eder, Sauer and Wiechert[11], the real impact started in the beginning of 2000, when the amino acid proline, was introduced for the first time as an enamine

[10] Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569.
[11] a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496-497. b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615-1621.

organocatalyst by List and Barbas.[12] They demonstrated the use of proline catalyst in the reaction of acetone with different aldehydes.

Iminium ion catalysis is the other earliest described organocatalytic activation mode. The condensation of a chiral amine with an α-β unsaturated carbonyl compound forms an iminium ion, which is more electrophilic than the initial aldehyde or ketone (Scheme 1.2).[13] Lowering the energy of the LUMO (Lowest Unoccupied Molecular Orbital) diminishes the orbital gap and facilitates the nucleophilic additions. This concept was first introduced by MacMillan in 2000, in the Diels-Alder reaction of α-β unsaturated aldehydes with different dienes.[14]



Scheme 1.2. Enamine and Iminium ion activation modes.

Enamine catalysis and iminium catalysis both involve the use of chiral amines to activate carbonyl compounds. Enamine catalysis takes advantage of the HOMO (Highest Occupied Molecular Orbital) raising effect, generating a nucleophilic enamine species from a carbonyl compound. This reactive intermediate is then suitable for α-functionalization with different electrophiles. On the other hand, iminium ion catalysis has the LUMO lowering effect which generates electrophilic iminium species from α,β-unsaturated carbonyl compounds suitable for β-functionalization with a variety of nucleophiles.[15]

[12] List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395-2396.
[13] Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416-5470.
[14] Ahrendt, A. K.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2000**, *122*, 4243-4244.
[15] Beeson, D. T.; Mastracchio, A.; Hong, J; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582-585.

Apart from enamine-iminium ion activation modes, in 2007, a new activation mode was introduced by MacMillan *et al.* which is called SOMO (Singly Occupied Molecular Orbital Catalysis) activation catalysis. SOMO catalysis refers to the formation of radical cations of enamine intermediates in the presence of a mild oxidant, allowing the transient electron rich enamines to react with weakly nucleophilic substrates. The concept would soon be extended by the same group to the enantioselective α-enolation of aldehydes.[16]

There are also some examples of non-amino Lewis base organocatalysts like phosphines and NHC (*N*-heterocyclic carbenes). Phosphines have been widely used as ligands for transition metal catalyzed reactions, but phosphorus Lewis base organocatalysts have been shown to promote the acylation of alcohols,[17] Morita-Baylis-Hillman,[18] annulation of allenes with different substrates,[19] allylic substitution[20] and intramolecular γ-addition of oxygen nuclophiles to alkynyl esters.[21] *N*-heterocylic carbenes have also been used both in transition metal catalysis and organocatalysis. The working principle of NHC organocatalysis is based on polarity inversion (umpolung), with the addition of NHC catalysts to aldehydes generate a reactive acyl anion equivalent in the form of a Breslow intermediate.[22] NHC organocatalysts are usually generated in situ from their ionic precursors, like imidazolium, thiazolium and triazolium salts which are deprotonated in the reaction media. Applications such as the benzoin condensation,[23] Stetter reaction[24] and homoenolate reactions[25] are well known in the literature.

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[16] Jang, H. Y.; Hong, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2007**, *129*, 7004-7005.
[17] Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430-431. b) Vedejs, E.; MacKay, J. A. *Org. Lett*. **2001**, *3*, 535-536.
[18] Shi, M.; Chen, L. H. *Chem. Commun*. **2003**, *11*, 1310-1311. b) Shi, M.; Chen, L. H.; Teng, W. D. *Adv. Synth. Catal*. **2005**, *347*, 1781-1789. c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614-4628. d) Shi, Y. L.; Shi, M. *Adv. Synth. Catal*. **2007**, *349*, 2129-2135.
[19] Zhang, C.; Lu, X. *J. Org. Chem.*, **1995**, *60*, 2906-2908. b) Xu, Z.; Lu, X. *J. Org. Chem*. **1998**, *63*, 5031-5041.
[20] Bertenshaw, S.; Kahn, M. *Tetrahedron Lett*. **1989**, *30*, 2731-2732. b) Cho, C. W.; Krische, M. J. *Angew. Chem., Int. Ed*. **2004**, *43*, 6689-6691. c) Ma, G. N.; Cao, S. H.; Shi, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1086-1092.
[21] Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed*. **2009**, *48*, 2225-2227. b) Sinisi, R.; Sun, J.; Fu, G. C. *Proc. Nat. Acad. Sci*. **2010**, *48*, 20652-20654.
[22] Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev*. **2007**, *107*, 5606-5655. b) Biju, A. T.; Kuhl, N.; Glorius, F. *Accts. Chem. Res*. **2011**, *44*, 1182-1195. c) Bugaut, X.; Glorius, F. *Chem. Soc. Rev*. **2012**, *41*, 3511-3522.
[23] Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed*. **2002**, *41*, 1743-1745. b) Mennen, S. M.; Miller, S. J. *J. Org. Chem.* **2007**, *72*, 5260-5269 c) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem*. **2009**, *74*, 9214-9217.

1.1.2. Lewis Acid Catalysis

Lewis acid catalysts are in general metal-based species which act as electron pair acceptors, activating the substrates toward nucleophilic attack. When it is considered in organic catalysis, Phase-Transfer Catalysis (PTC) (Figure 1.3.) can also be classified as Lewis acid catalysis[26] although they have a distinct reactivity and activation mode, promoting reactions by increasing the solubility of reagents in biphasic reaction solutions and helping the transfer of molecules or ions from one phase to another.[27] Asymmetric phase-transfer catalysis has been used in several different reactions like alkylation,[28] Michael addition,[29] Aldol condensation,[30] etc. with great success.

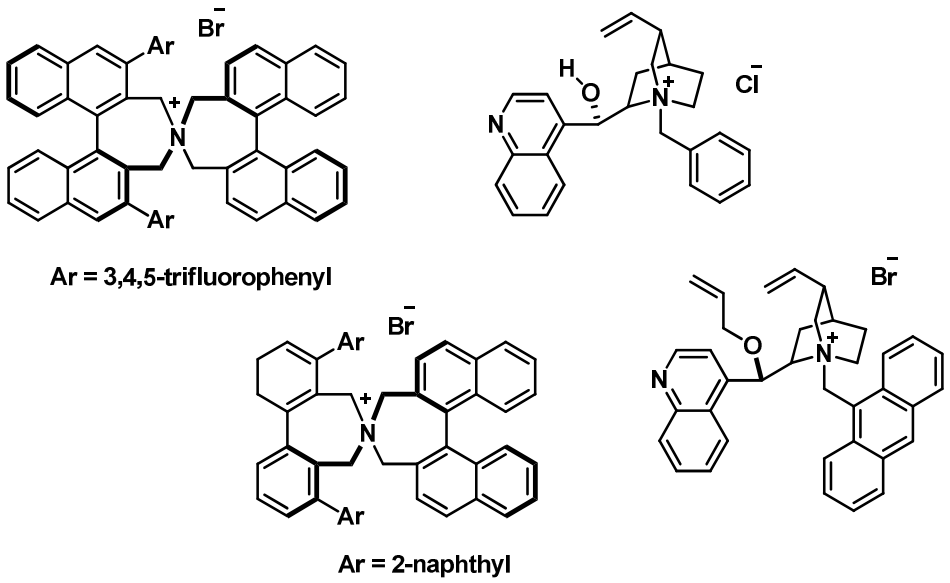

Figure 1.3. Some Phase Transfer Catalysts.

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[24] Enders, D.; Han, J.; Henseler, A. *Chem. Commun*. **2008**, *34*, 3989-3991. b) DiRocco, D. A.; Oberg, K. M.; Dalton, D. M.; Rovis, T. *J. Am. Chem. Soc*. **2009**, *131*, 10872-10874.
[25] Sohn, S. S.; Rosen, E. L.; Bode, W. J. *J. Am. Chem. Soc*. **2004**, *126*, 14370-14371. b) Nair, V.; Menon, R. S.; Biju, A. T.; Sinu, C. R.; Paul, R. R.; Jose, A.; Sreekumar, V. *Chem. Soc. Rev*. **2011**, *40*, 5336-5346.
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[29] Zhang, F. Y.; Corey, E. J. *Org. Lett*. **2000**, *2*, 1097-1100.
[30] Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed*. **2002**, *41*, 4542-4544. b) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem Soc*. **2004**, *126*, 9685-9694.

1.1.3. Brønsted Base Catalysis

Brønsted base (BB) and Brønsted acid (BA) catalytic cycles are initiated via deprotonation or protonation, in contrast to Lewis acid (LA) and Lewis base (LB) catalysis. The former has played an important role to promote a great number of reactions[31] and a common feature in BB catalysts is the presence of nitrogen containing functional groups, with tertiary amines, guanidines, amides, imidazoles and *Cinchona* alkaloids being well-known examples. Additionally, with the introduction of H-bond donating groups, the concept of bifunctional catalysis[32] was developed (Figure 1.4) and brought the field into new grounds.

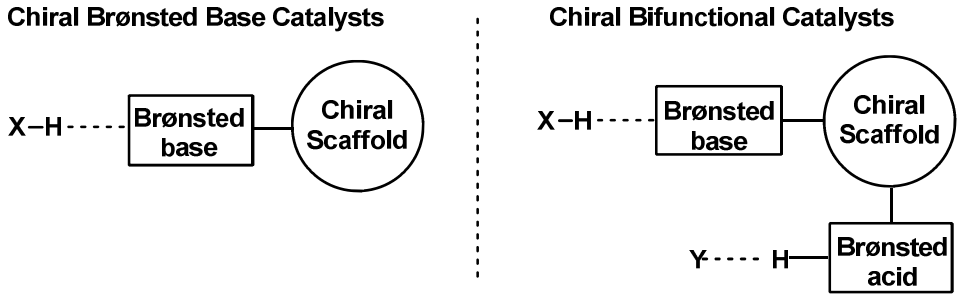


Figure 1.4. Chiral Brønsted base catalysis.[32]

Bifunctional BB catalysts deprotonate substrates, forming positively charged amines ionically paired with the negatively charged nucleophile in the transition state. Thus, they are also classified under the heading of non-covalent bonding catalysis (Figure 1.5).

[31] France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev*. **2003**, *103*, 2985-3012. b) Ting, A.; Goss, J. M.; McDougal, N. T.; Schaus, S. E. *Top. Curr. Chem. Springer-Verlag Berlin Heidelberg* **2009**, *291*, 145–200. c) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev*. **2009**, *38*, 632-653.
[32] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672-12673. b) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett*. **2004**, *6*, 625-627. c) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett*. **2005**, *7,* 4713-4716. d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, *35*, 4481-4483 e) Connon, S. J. *Chem. Commun.* **2008**, *22*, 2499-2510.

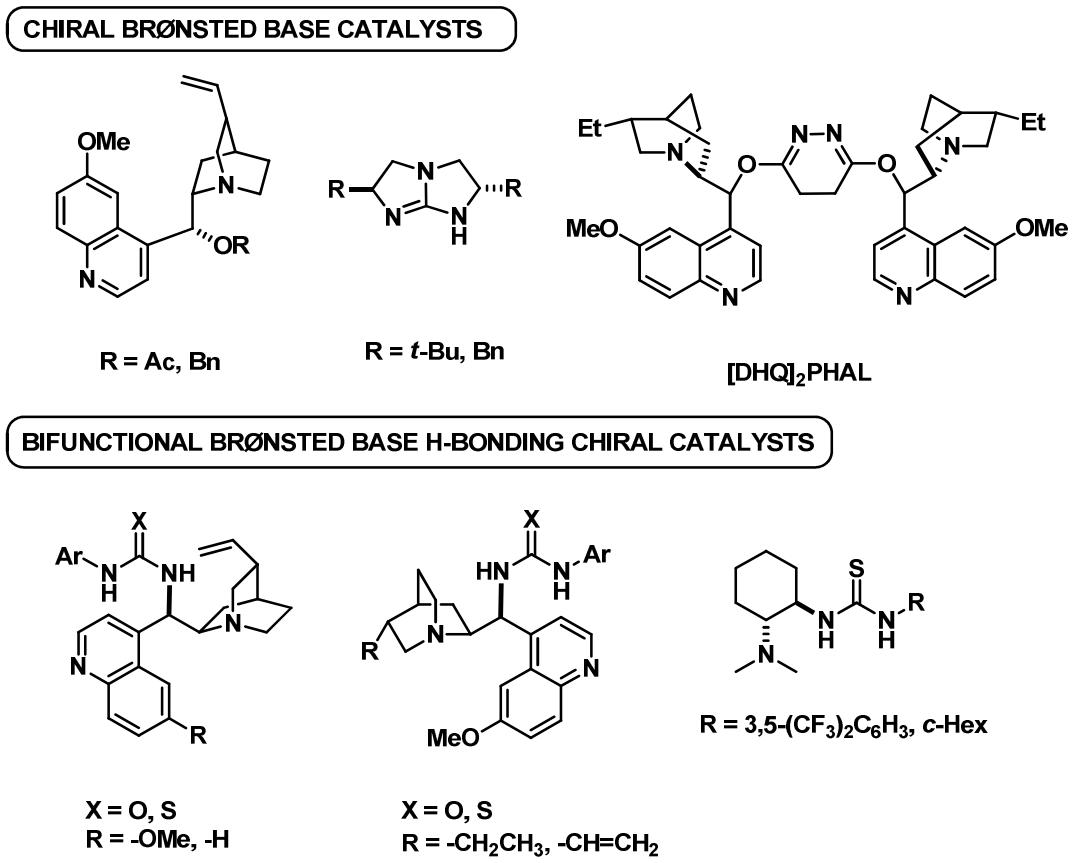
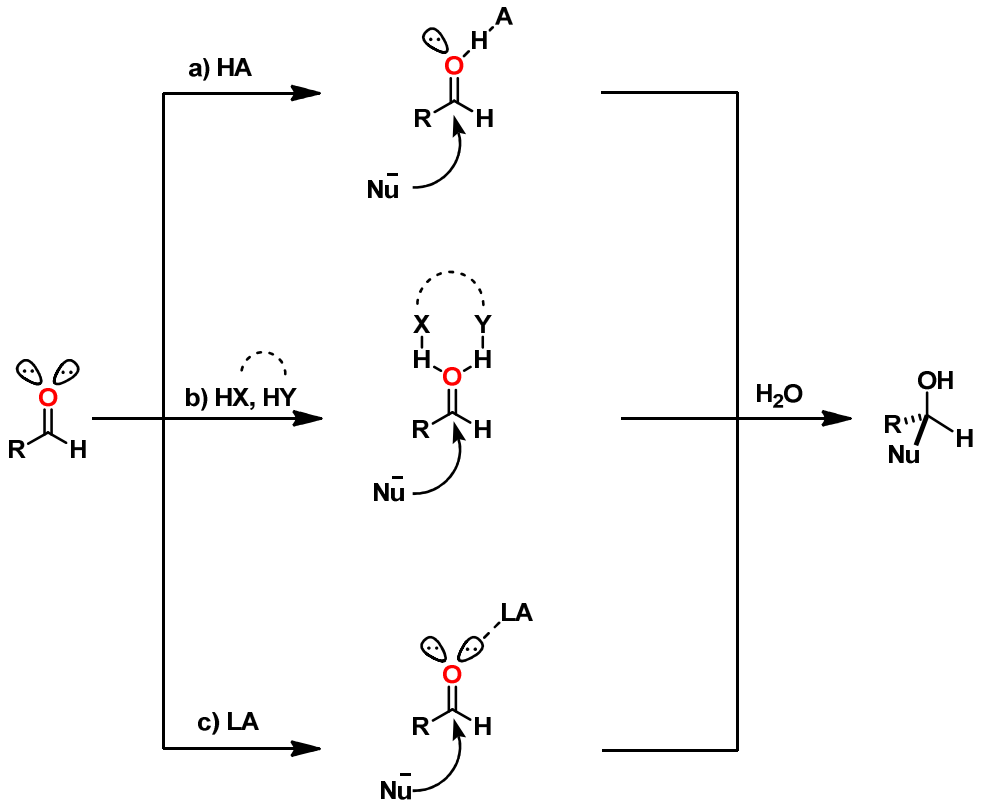


Figure 1.5. Chiral Brønsted base catalysts.

1.1.4. Brønsted Acid Catalysis

Compared to more established Lewis acid counterparts, Brønsted acid catalysts are a relatively younger group of organocatalysis. Even though metal combined Lewis acids are well-known reactive and powerful species for asymmetric synthesis, there are some drawbacks associated to their use like toxicity, sensitivity, cost, *etc*. BA organocatalysts, like LA organocatalysts coordinate to the substrate to lower the energy of the LUMO thus activating it for nucleophilic attack (Scheme 1.3). Luckly, due to the lack of metallic species this is in most cases an environmentally friendlier approach.[8,33]

[33] a) Schreiner, P. R. *Chem. Soc. Rev*. **2003**, *32*, 289-296. b) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062-2064.



Scheme 1.3. a) Single hydrogen-bond activation b) Double hydrogen bond activation and c) LA activation of carbonyl compounds by coordination.

Chiral Brønsted acid catalysts are able to promote many different reactions such as Mannich,[34] Friedel-Crafts,[35] Pictet-Spengler,[36] Strecker,[37] transfer hydrogenations[38] and cycloaddition[39] reactions. The most successful catalysts in this type of activation include chiral BINOL phosphates, BINOL derived *N*-triflyl phosphoramides, ureas/thioureas, and alcohols (Figure 1.6).

[34] a) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc*. **2004**, *126*, 5356-5357. b) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756-6764. c) Tillmana, A. L.; Dixon, D. J. *Org. Biomol. Chem*. **2007**, *5*, 606-609. d) Schenker, S.; Zamfir, A.; Freund, M.; Tsogoeva, S. B. *Eur. J. Org. Chem*. **2011**, *12*, 2209-2222.
[35] a) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc*. **2007**, *129*, 292-293. b) You, S. L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev*. **2009**, *38*, 2190-2201. c) Rueping, M.; Raja, S.; Núñez, A. *Adv. Synth. Catal*. **2011**, *353*, 563-568.
[36] a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2004**, *126*, 10558-10559. b) Klausen, R. S.; Jacobsen, E. N. *Org. Lett*. **2009**, *11*, 887-890. c) Rueping, M.; Volla, C. M. R. *RSC Advances* **2011**, *1*, 79-82.
[37] a) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2000**, *39*, 1279-1281. b) Rueping, M.; Sugiono, E.; Azap, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 2617-2619. c) Zhang, G. W.; Zheng, D. H.; Nie, J.; Wang, T.; Ma, J. A. *Org. Biomol. Chem*. **2010**, *8*, 1399-1405.
[38] a) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett*. **2005**, *7*, 3781-3783. b) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed*. **2007**, *46*, 4562-4565.
[39] a) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc*. **2006**, *128*, 9626-9627. b) Rueping, M.; Raja, S. *Beilstein J. Org. Chem*. **2012**, *8*, 1819-1824.

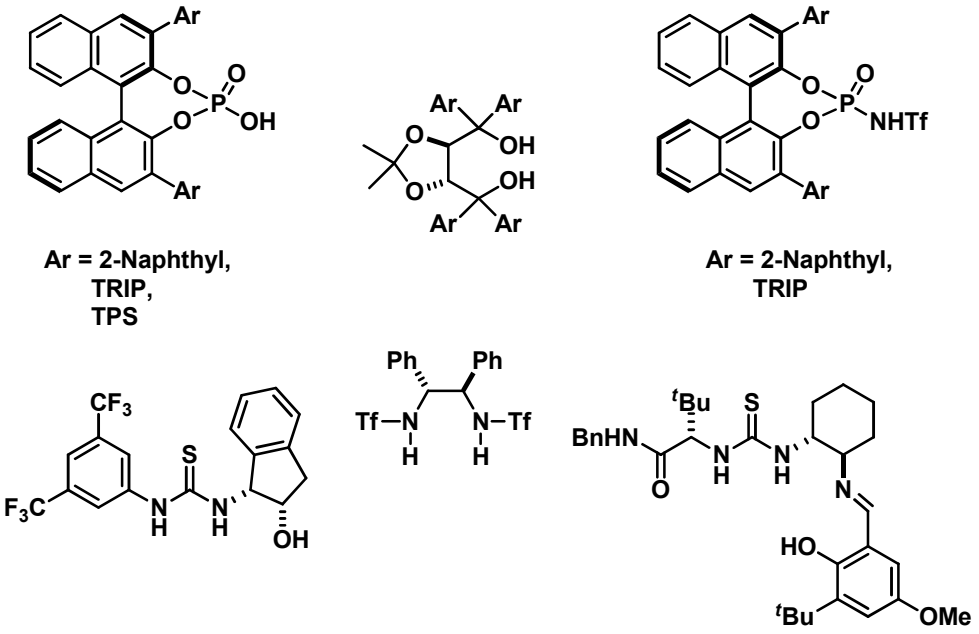


Figure 1.6. Chiral Brønsted acid catalysts.

1.2. SUPPORTED CATALYSTS

Catalysis is one of the pillars of the chemical industry. Indeed, the use of homogeneous and heterogeneous catalysts has played a key role in the development of more efficient strategies for organic synthesis. For years, asymmetric homogeneous catalysts have been used for the synthesis of enantiopure compounds to fulfill the increasing need of academia and industry. However, growing demand of these enantiopure compounds has brought out problems in the synthesis process like high costs, sensitivity, metal leaching, difficulties in separation and recyclability of the asymmetric homogeneous catalysts.[40] Immobilized asymmetric homogeneous catalysts are designed to overcome these challenges while maintaining the reactivity and selectivity profiles of their homogeneous counterparts.

Catalyst immobilization is described as "*the conversion of homogeneous catalysts to heterogeneous species, which are capable of being separated from the reaction mixture and preferably be reused for multiple times*".[41a] With the immobilization of chiral catalysts on solid supports the focus is set on combining the positive properties of homogeneous catalysts with the additional stability, recyclability and separation properties of heterogeneous catalysts. However, there

[40] a) Ding, K.; Uozumi, Y. *Handbook of Asymmetric Heterogeneous Catalysis*, *Wiley-VCH, Weinheim*, **2008**. b) De Vos, D. E.; Van-kelecom, I. F. J.; Jacobs, P. A. *Chiral Catalyst Immobilization and Recycling, Wiley-VCH, Weinheim*, **2000**.

are several precautions to be taken into consideration during this immobilization process to generate reactive and efficient supported catalysts. These involve the choice of a support, linker, spacer, and functionalization level, which are the parameters that will mainly affect the activity of the catalysts (Figure 1.7).[41] The interactions between the catalysts and supports must be restricted to avoid deleterious interactions with the active sites. This separation is provided by the linker or spacer, which are selected to be chemically inert in the reaction conditions.

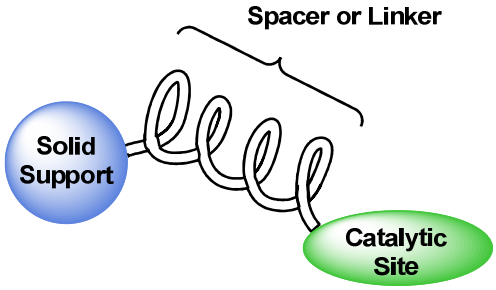


Figure 1.7. General design of solid supported catalysts.

Immobilization of asymmetric homogeneous catalysts can be classified under two different main categories: heterogenized catalysts and non-conventional media catalysts (Figure 1.8) which can be further divided in many subcategories.[41a]

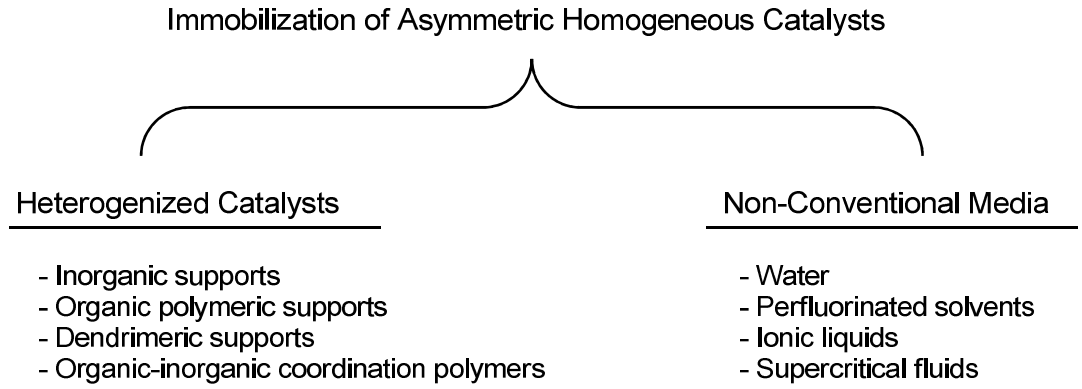


Figure 1.8. Immobilization of asymmetric homogeneous catalysts.

[41] a) Heitbaum, M.; Glorius, F.; Escher, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 4732-4762. b) Cozzi, F. *Adv. Synth. Catal.* **2006**, *348*, 1367-1390.

1.2.1. Immobilization of Asymmetric Homogeneous Catalysts: Catalyst Heterogenization

Catalysts heterogenization can be done either through covalent or non-covalent interactions (Figure 1.9.) but covalent immobilization is the most preferential way due to stronger binding between the homogeneous catalysts and supports. Non-covalent interactions such as adsorption, electrostatic interactions and entrapment immobilizations have also been used but they are not so convenient due to weak interactions, catalyst leaching, instability and pore size problems of entrapment immobilization techniques.[41a]

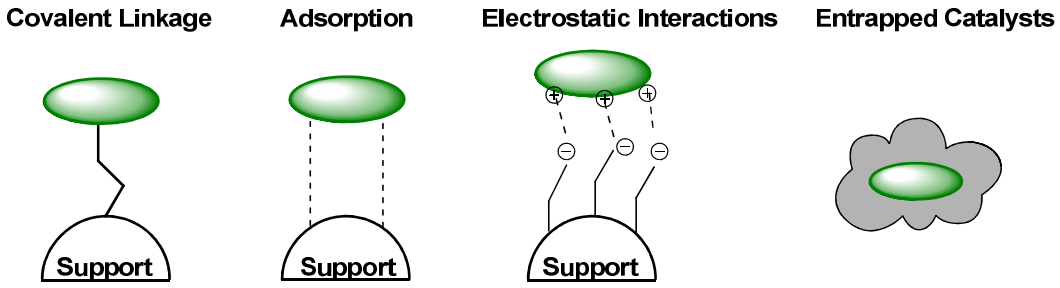


Figure 1.9. Immobilization strategies of chiral homogeneous catalysts.

Consequently, in this thesis we will mainly focus on covalent immobilization of chiral homogeneous catalysts, which is the most common strategy. To anchor the homogeneous catalysts to a solid support some modifications (functionalization) are necessary on either the catalyst or the support. All the general precautions mentioned under the headings of supported catalysts have to be considered for covalently immobilized catalysts, too. As general support type, polymers,[42] inorganic oxides,[43] and nanoparticles,[44] among others, are used efficiently in the literature.

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[42] a) Pu, L. *Chem. Eur. J.* **1999**, *5*, 2227-2232. b) Song, C. E.; Yang, J. W.; Roh, E. J.; Lee, S.-G.; Ahn, J. H.; Han H. *Angew. Chem., Int. Ed*. **2002**, *41*, 3852-3854. c) Benaglia, M.; Puglisi, A.; Cozzi, F. *Chem. Rev*. **2003**, *103*, 3401-3430.
[43] a) Ying, J. Y.; Mehnert, C. P.; Wong, M. S. *Angew. Chem., Int. Ed*. **1999**, *38*, 56-77. b) Alcón, M. J.; Corma, A.; Iglesias, M.; Sánchez, F.; *J. Organomet. Chem*. **2002**, *655*, 134-145. c) Tao, Y.; Kanoh, H.; Abrams, L.; Kaneko, K. *Chem. Rev*. **2006**, *106*, 896-910.
[44] a) Tamura, M.; Fujihara, H. *J. Am. Chem. Soc*. **2003**, *125*, 15742-15743. b) Hu, A.; Yee, G. T.; Lin, W. *J. Am. Chem. Soc*. **2005**, *127*, 12486-12487. c) Wildgoose, G. G.; Banks, C. E.; Compton, R. G. *Small* **2006**, *2*, 182-193. d) Corma, A.; Garcia, H. *Chem. Soc. Rev*. **2008**, *37*, 2096-2126.

1.2.1.1. Asymmetric Catalysts Covalently Immobilized on Polymeric Resins

Polymeric resins were introduced by Merrifield in the 1960s in the area of solid phase peptide synthesis[45] and the first examples were based on polystyrene (PS), using divinylbenzene (DVB) as the cross-linker. Resins can have different structures and these differences make them either soluble or insoluble supports. One important property for polymers is 'cross-linking' which involves the formation of a bond that connects one polymer chain to another, and gives different physical properties to the polymer.[46] There are alternatives to the pioneering Merrifield resin, like the one commercially called JandaJEL® which contains flexible tetrahydrofuran-derived cross-linking[47] and TentaGel® resin (polystyrene-polyethyleneglycol) that has an ethylene glycol cross-linking unit (Figure 1.10). These differences in structure allow the resins to swell in different media.

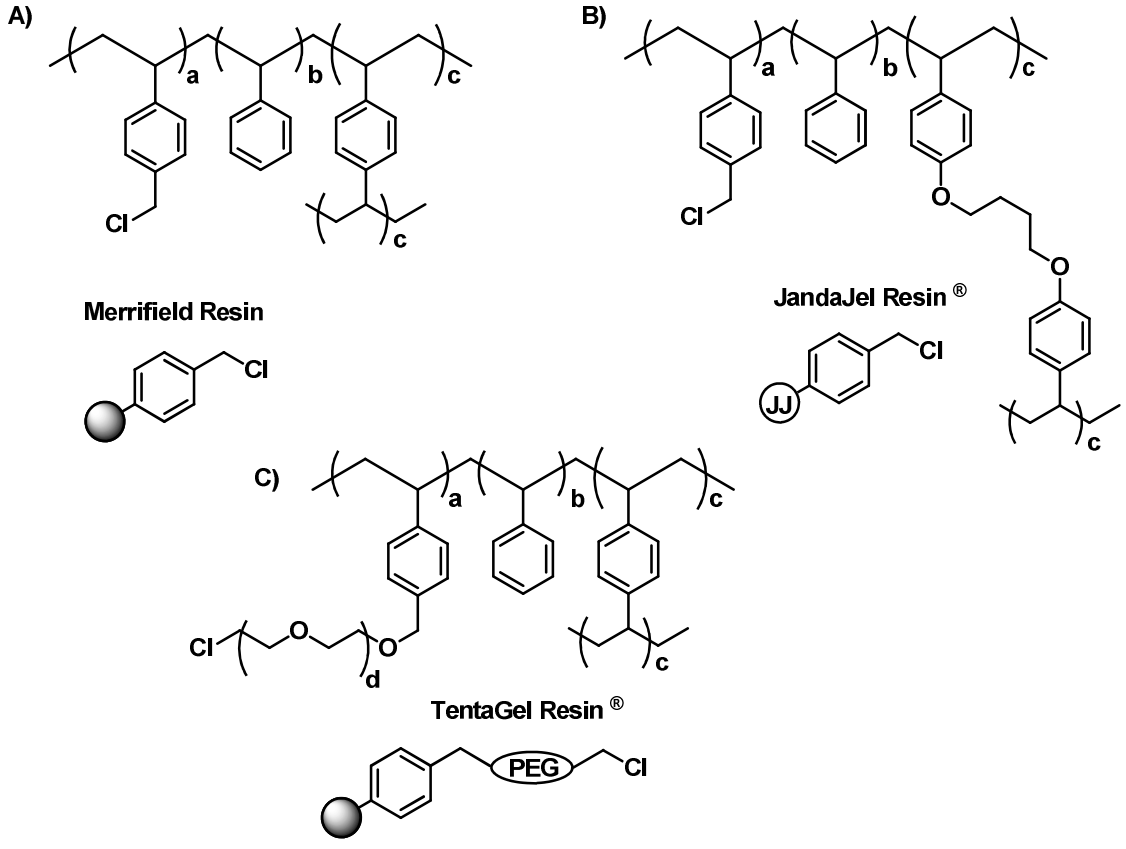
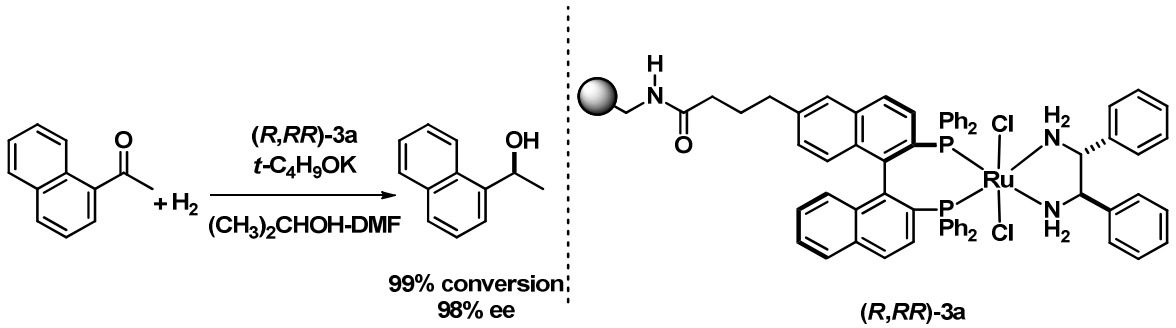


Figure 1.10. Representation of A) Merrifield resin, B) JandaJEL® and C) TentaGel® resin

[45] Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.
[46] IUPAC, "*Glossary of basic terms in polymer science 1996*" *Pure and Applied Chemistry* **1996**, *68*, 2287-2311.
[47] Toy, P. H.; Janda, K. D. *Tetrahedron Lett.* **1999**, *40*, 6329-6332.

The advantages of the immobilization of chiral catalysts on polymeric resins are easy recovery, reusability; in most cases the polymeric support gives robustness to the catalysts for successive uses. In the literature there are several examples of metal-ligand polymer complexes and one of the successful applications was done by Noyori *et al*., who developed Ru-BINAP-diamine immobilized catalyst for the hydrogenation of ketones. This immobilized catalyst proved as reactive as the homogeneous BINAP catalyst and it could be recycled up to 10 times with only a slight decrease in the conversion (Scheme 1.4).[48]



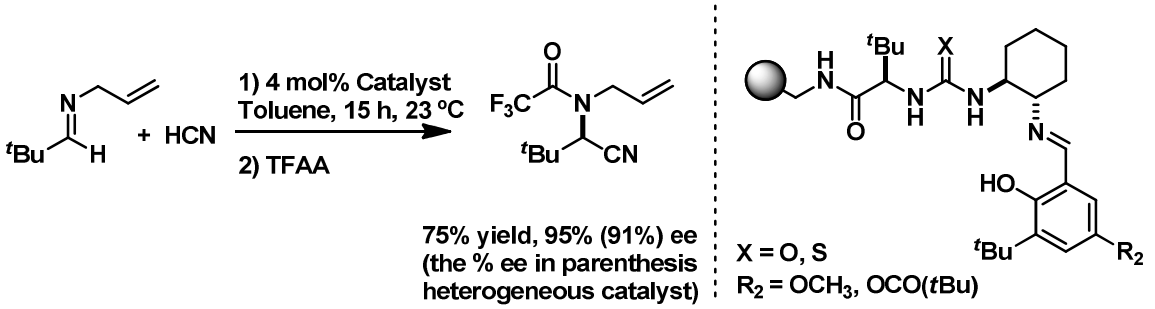
Scheme 1.4. Asymmetric hydrogenation of ketones by polymer-bound Ru complex.

The strategy of anchoring metal-ligand complexes onto polymers has been used in several different transformations[49] like asymmetric hydrogenation,[42,50] asymmetric hydroformylation,[51] asymmetric epoxidation,[52] asymmetric allylic substitution,[53] etc. The increase in cost associated with these anchoring strategies has been compensated by recycling the immobilized catalysts while diminishing the leaching of the metallic centers, which is one of the main concerns of pharmaceutical industry.

Organocatalysts are also suitable for anchoring onto polymers.[45c] Depending on the reaction conditions different types of polymer supports can be used. Jacobsen *et al.* developed the first polymer-supported urea and thiourea organocatalysts for the asymmetric hydrocyanation of imines (Strecker reaction)

[48] Ohkuma, T.; Takeno, H.; Honda, Y.; Noyori, R. *Adv. Synth. Catal*. **2001**, *343*, 369-375.
[49] a) Clapham, B.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637-4662. b) Fan, Q. H.; Li, Y. M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385-3466.
[50] ter Halle, R.; Colasson, B.; Schulz, E.; Spagnol, M.; Lemaire, M. *Synlett* **2000**, *5*, 680-682.
[51] a) Nozaki, K.; Itoi, Y.; Shibahara, F.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *J. Am. Chem. Soc*. **1998**, *120*, 4051-4052. b) Nozaki, K.; Shibahara, F.; Itoi, Y.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 1911-1918.
[52] a) De, B. B.; Lohray, B. B.; Dhal, P. K. *Tetrahedron Lett*. **1993**, *34*, 2371-2374. b) Smith, K.; Liu, C. H. *Chem. Commun*. **2002**, 8, 886-887.
[53] a) Gamez, P.; Dunjic, B.; Fache, F.; Lemaire, M. *J. Chem. Soc., Chem. Commun.* **1994**, *12*, 1417-1418. b) Hallman, K.; Moberg, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1475-1478.

(Scheme 1.5).[54] They reported that these polymer supported species provide easy purification of product by simple filtration and solvent evaporation. Moreover, the catalyst could be recycled without loss of reactivity and enantioselectivity.



Scheme 1.5. Asymmetric Strecker reaction with polymer supported urea and thiourea organocatalysts.

1.2.1.2. Non-Covalently Immobilized Asymmetric Catalysts

The use of covalently immobilized catalysts or their non-covalent immobilized counterparts completely depends on the nature of the reaction they are applied to. Although non-covalently supported catalysts have weaker interactions, they can be used to form metal-ligand solid-supported species or supported organocatalysts.[41,42a,55] Immobilization can be done by adsorption, electrostatic interactions or entrapment (Figure 1.9).

Similar to covalently immobilized catalysts, there are some successful and some inefficient examples in the literature for the non-covalent strategy. They have been used in different reactions and chiral Mn(III)salen complexes are one of the most studied, especially for the asymmetric epoxidation. In the literature there are several examples of polymer supported, encapsulated, and ion exchange immobilized chiral Mn(III)salen-catalyzed[42a,51b,56] asymmetric epoxidation reactions. When the molecular sieves pores were used for immobilization of Mn-salen complexes, metal leaching in the reaction was lowered but the reaction had lower enantioselectivity.[57] With the ion-exchange method, Mn-salen complexes were immobilized on 10-montmorillonite-clay-type commercial supports, and in

[54] a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1998**, *120*, 4901-4902. b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279-1281.
[55] Zhang, L.; Luo, S.; Cheng, J. P. *Catal. Sci. Technol.* **2011**, *1*, 507-516.
[56] Xia, Q. H.; Ge, H. Q.; Ye, C.P.; Liu, Z. M.; Su, K. X. *Chem. Rev*. **2005**, *105*, 1603-1662.
[57] a) Frunza, L.; Kosslick, H.; Landmesser, H.; Höft, E.; Fricke, R. *J. Mol. Catal. A: Chem*. **1997**, *123*, 179-187. b) Piaggio, P.; Langham, C.; McMorm, P.; Bethell, D.; Bulman-Page, P. C.; Hancock, F. E.; Sly, C.; Hutchings, G. J. *J. Chem. Soc., Perkin Trans. 2* **2000**, *1*, 143-148.

that case again the supported catalysts gave lower ee.[58] By using the entrapment methodology Zeolite type supports could also be used and in some cases catalysts showed ee's as high as the ones obtained with the homogeneous version.[59]

However, this strategy of anchoring homogeneous catalysts on solid supports either by covalent or non-covalent means is not always working with full efficiency. Immobilized catalysts may show lower reactivity when compared to their homogeneous counterparts due to the bulk structure of the support. For some cases, this structure does not allow proper interaction between the catalytic active sites and the reactants. To prevent this problem, a great importance has to be assigned on the choice of linker and the possible undesired interactions between the catalyst and the solid support have to be considered. However, despite these possible drawbacks, the advantages of immobilized catalysts, exemplified in many successful applications, still make these catalysts desirable for use.

The immobilization of asymmetric catalysts is still a fresh topic for chemists. Until now, great efforts have been devoted for improving the immobilization strategies; new support types have been developed in an evolution that is likely to continue due to its connection with sustainable chemistry. Our laboratory is one of the research groups that has been working on this area for many years and has great experience on immobilization of both organometallic ligands and organocatalysts onto solid supports. The organometallic catalysts developed in the group are mostly immobilized on polystyrene and in many cases they have been applied to asymmetric alkyl or aryl zinc addition reactions (Figure 1.11).[60]

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[58] Fraile, J. H.; Garcia, J. I.; Massam, J.; Mayoral, J. A. *J. Mol. Catal. A: Chem.* **1998**, 136, 47-57.
[59] a) Ogunwumi, S. B.; Bein, T. *Chem. Commun*. **1997**, 9, 901-902. b) Sabater, M. J.; Corma, A.; Domenech, A.; Fornes, V.; Garcia, H. *Chem. Commun*. **1997**, 14, 1285-1286.
[60] Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309-6318. b) Pericàs, M. A.; Castellnou, D.; Rodríguez, I.; Riera, A.; Solà, L. *Adv. Synth. Catal.* **2003**, *345*, 1305-1313. c) Castellnou, D.; Solà, L.; Jimeno, C.; Fraile, J. M.; Mayoral, J. A.; Riera, A.; Pericàs, M. A. *J. Org. Chem*. **2005**, *70*, 433-438. d) Castellnou, D.; Fontes, M.; Jimeno, C.; Font, D.; Solà, L.; Verdaguer, X.; Pericàs, M. A. *Tetrahedron* **2005**, *61*, 12111-12120. e) Bastero, A.; Font, D.; Pericàs, M. A. *J. Org. Chem.* **2007**, *72*, 2460-2468. f) Popa, D.; Marcos, R.; Sayalero, S.; Vidal-Ferran, A.; Pericàs, M. A. *Adv. Synth. Catal*. **2009**, *351*, 1539 - 1556. g) Marcos, R.; Jimeno, C.; Pericàs, M. A. *Adv. Synth. Catal*. **2011**, *353*, 1345-1352. h) de la Fuente, V.; Marcos, R.; Cambeiro, X. C.; Castillón, S.; Claver, C.; Pericàs, M. A. *Adv. Synth. Catal.* **2011**, *353*, 3255-3261 i) Osorio-Planes, L; Rodríguez-Escrich, C.; Pericàs, M. A. *Org. Lett*. **2012**, *14*, 1816-1819. j) Ozkal, E.; Özçubukçu, S.; Jimeno, C.; Pericàs, M. A. *Catal. Sci. Technol*., **2012**, *2*, 195-200.

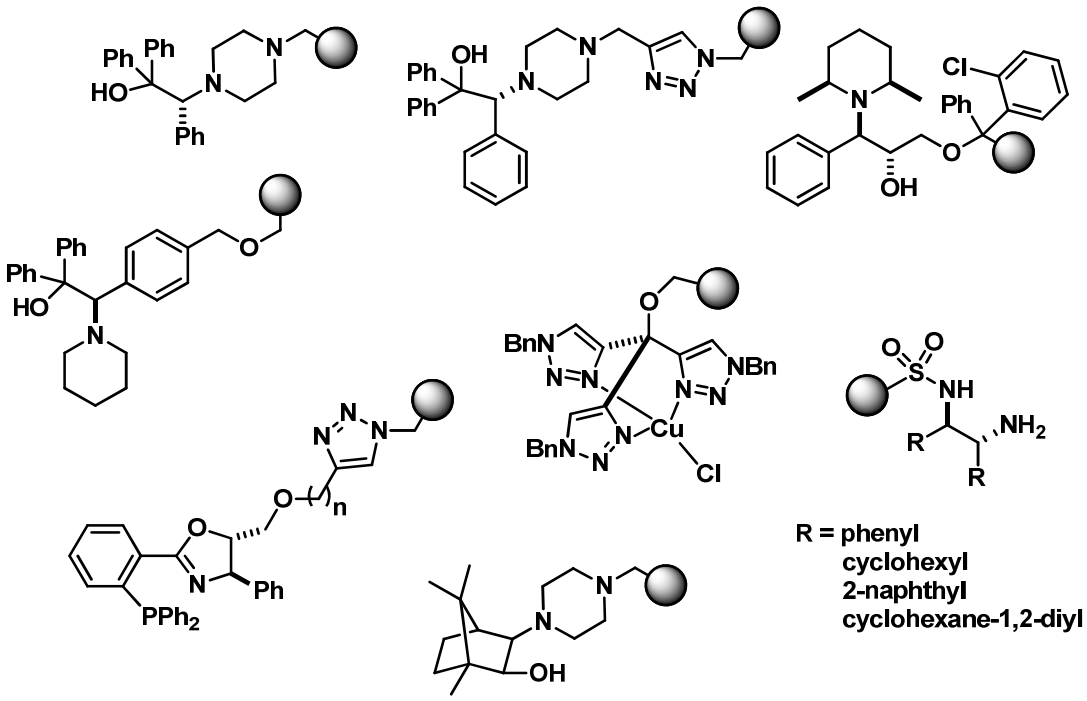


Figure 1.11. Structure of polymer supported ligands developed in the Pericàs group.

A few years ago, the golden rush of organocatalysis, promted us to start a new research line, and several organocatalysts were anchored to polystyrene successfully (Figure 1.12). Derivatives of proline, pyrrolidine, diarylprolinol ethers, imidazoline and H-bonding squaramide organocatalysts[61] have been immobilized in this research line. A common feature between most of the supported ligands and organocatalysts is the strategy followed for immobilization: in both cases, the triazole linker is used for covalent immobilization of the homogeneous catalysts to the solid supports. These triazole linkers have been introduced with the "click reaction", also known as azide-alkyne cycloaddition reaction (AAC).

[61] a) Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653-4655. b) Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2007**, *9*, 1943-1946. c) Alza, E.; Cambeiro, X. C.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2007**, *9*, 3717-3720. d) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett*. **2008**, *10*, 337-340. e) Alza, E.; Rodríguez-Escrich, C.; Sayalero, S.; Bastero, A.; Pericàs, M. A. *Chem. Eur. J.* **2009**, *15*, 10167-10172. f) Alza, E.; Pericàs, M. A. *Adv. Synth. Catal*. **2009**, *351*, 3051-3056. g) Alza, E.; Sayalero, S.; Cambeiro, X. C.; Martín-Rapún, R.; Miranda, P. O.; Pericàs, M. A. *Synlett* **2011**, *4*, 464-468. h) Alza, E.; Sayalero, S.; Kasaplar, P.; Almaşi, D.; Pericàs, M. A. *Chem. Eur. J*. **2011**, *17*, 11585-11595. i) Ayats, C.; Henseler, A.; Pericàs, M. A. *ChemSusChem* **2012**, *5*, 320-325. j) Fan, X.; Sayalero, S.; Pericàs, M. A. *Adv. Synth. Catal*. **2012**, *354*, 2971-2976. k) Kasaplar, P.; Riente, P.; Hartmann, C.; Pericàs, M. A. *Adv. Synth. Catal*. **2012**, *354*, 2905-2910. l) Riente, P.; Yadav, J.; Pericàs, M. A. *Org. Lett*. **2012**, *14*, 3668-3671. m) Kasaplar, P.; Rodríguez-Escrich C.; Pericàs, M. A. *Org. Lett*. **2013**, *15*, 3498-3501.

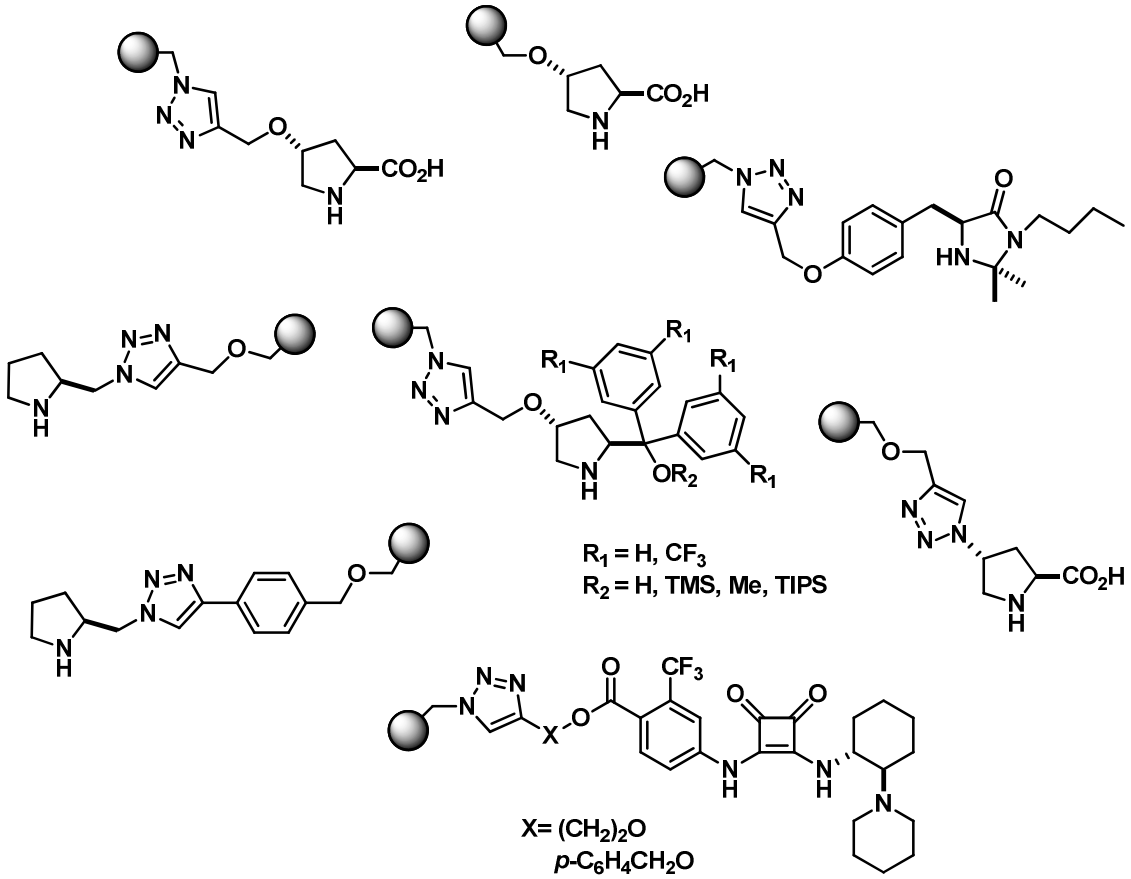


Figure 1.12. Structure of polymer-supported organocatalysts developed in the Pericàs group.

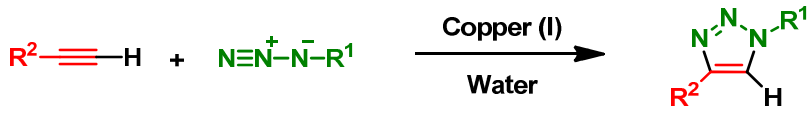
1.2.1.3. Copper-Catalyzed Azide-Alkyne Cycloaddition Reaction and 1,2,3-Triazole Moiety As Linker in Covalent Immobilization

Click chemistry was introduced by Kolb, Finn and Sharpless in 2001 and they conceptualized it as "*generating substances by joining small units together with heteroatom links*".[62] Since then, it has become one of the cornerstones of organic synthesis and also in time, it has become important for biological research. With the term "click chemistry", reactions are categorized according to their properties: to be "click" a reaction must have wide substrate scope, give high yields and require mild, simple reaction conditions, simple product isolation and use benign solvent.

The azide-alkyne cycloaddition (also known as Huisgen 1,3-dipolar cycloaddition) of alkynes and azides to form 1,2,3-triazole rings, is one of the well-

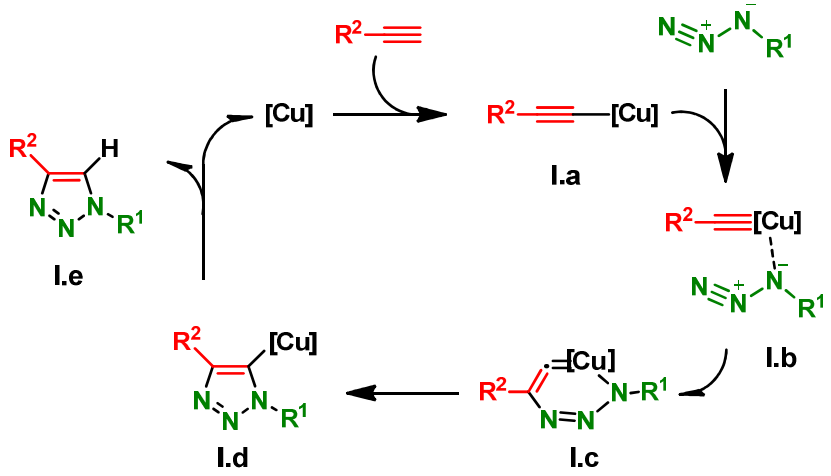
[62] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed*. **2001**, *40*, 2004-2021.

known examples of click reactions.[63] In 2002, the copper(I)-catalyzed reaction of terminal alkynes with azides to form 1,4-regioisomers of 1,2,3-triazoles (Scheme 1.6) was independently, reported by Sharpless *et al.* and Meldal *et al.*[64] This process is popularly known as the copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC).



Scheme 1.6. Copper-catalyzed azide-alkyne cycloaddition reaction (CuAAC).

CuAAC reaction starts with the formation of a Cu(I) acetylide species **I.a** enabled by the lower pK_a value of alkyne C-H proton after complexation. The C-N bond is formed between the vinylidene-like β-carbon of copper(I) acetylide and the electrophilic terminal nitrogen of the coordinated organic azide **I.b**. Complexation forms the metallacycle **I.c** which is then transformed to the triazole-copper derivative **I.d**. Finally, protonation of this triazole-copper derivative leads to the product formation **I.e** (Scheme 1.7).[64]



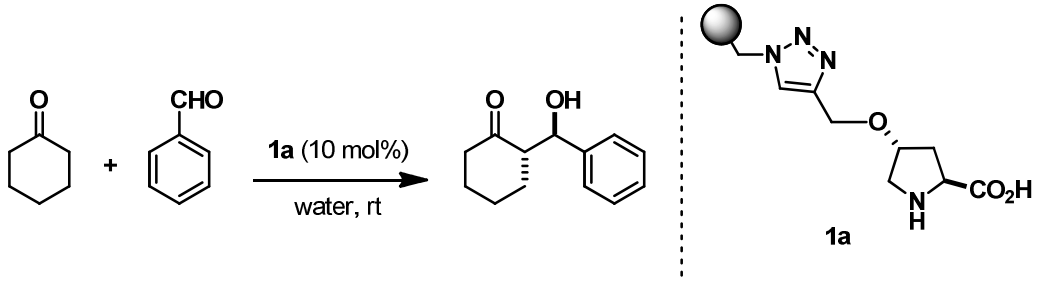
Scheme 1.7. Initially proposed mechanism for CuAAC.

CuAAC is a very convenient strategy for catalyst immobilization because of its ease, mild reaction conditions and easy monitoring of the reaction through IR.

[63] Huisgen, R. "Centenary Lecture - 1,3-Dipolar Cycloadditions". *Proceedings of the Chem. Soc. London* **1961**, 357-396.
[64] a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596-2599. b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064. c) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J. Org. Chem.* **2006**, *1*, 51-68. d) Hein, J. E.; Fokin, V. V. *Chem. Soc. Rev.* **2010**, *39*, 1302-1315. e) Díez-González, S. *Catal. Sci. Technol.* **2011**, *1*, 166-178.

However, it should be always foreseen that the triazole linker has to be inert under the reaction conditions and interactions with the catalyst active sites must be avoided. For example, in the immobilization of ligands for metal-catalyzed reactions, triazole units might coordinate to the metal, which can change the reactivity of the catalysts, and the reaction pathway in terms of enantioselectivity.[60e] On the other hand, it is also possible to see a positive effect through triazole coordination with the metal. Thus carefully designed ligands can exploit this metal-triazole interaction to generate the desired products in an enantioselective manner.[60h]

The situation is relatively similar with supported organocatalysts. As a linker, the triazole unit has to be orthogonal (not to restrict the catalytic activity). The experience of our research group on organocatalyst immobilization to solid supports has shown that CuAAC reaction is an efficient covalent technique. In most cases, triazole linkers do not interfere with the catalytic activity. Moreover, the only remarkable example of triazole linker affirmative effect on organocatalysis was presented by our research group with a PS-supported proline catalyzed aldol reaction in water (Scheme 1.8).[61d] The role of triazole linker was related to an increase in the swelling ability of the PS-support, probably through formation of a hydrogen bond-based aqueous microphase around the hydrophobic resin, which increased the catalytic activity.



Scheme 1.8. Aldol reaction in water catalyzed by a PS-supported proline derivative.

As we have previously mentioned, the main advantages of immobilized catalysts are simple recovery and recycling. Once the immobilized catalyst is as efficient as its homogenous counterpart, these basic advantages can be taken one step forward. Indeed, one of the main features of immobilized catalysts is the possibility of implementing continuous flow operations.

1.3. CONTINUOUS FLOW CHEMISTRY

Continuous flow chemistry has recently gained great attention as it is perceived as a "*green*" approach, since it allows safer reaction conditions and controls, integrated synthesis, easy scale-up, faster reaction times and cleaner products. All these features make it more environmental friendly when compared to traditional organic synthesis. With the use of immobilized reagents and catalysts, the reputation of continuous flow chemistry has been upgraded and opens a door for industrial use and large scale production.[65]

Continuous flow operations are more effective than simple batch conditions in terms of reactivity. Flow-through columns or microreactors provide maximum contact between reactants in a smaller reaction area and give higher yield, products being easily and continuously separated from the reaction media. Ease of reaction control can be advantageous in case of dangerous reaction conditions. Even multi-step syntheses are possible under continuous flow conditions, without work-up or isolation of intermediate products, which saves time, money and space in an industrial scale (Figure 1.13).[66]

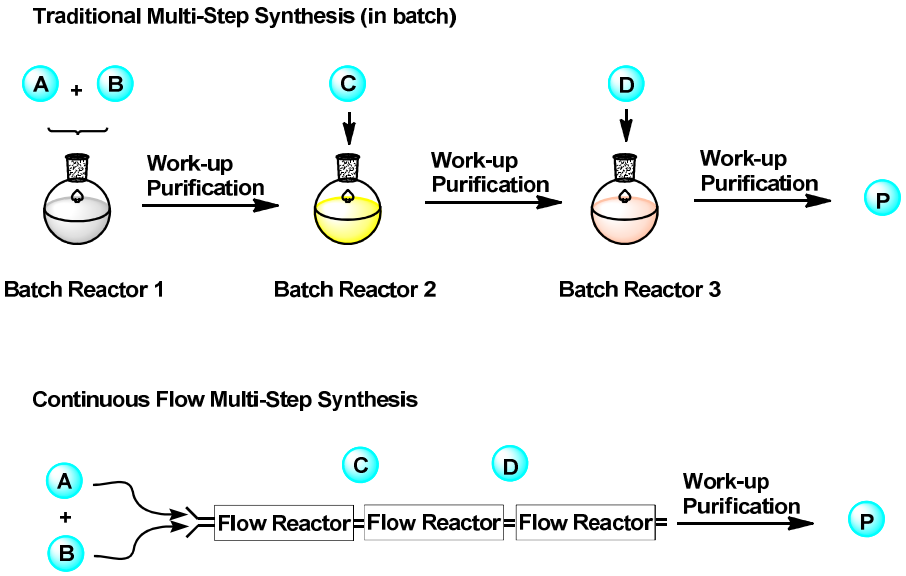
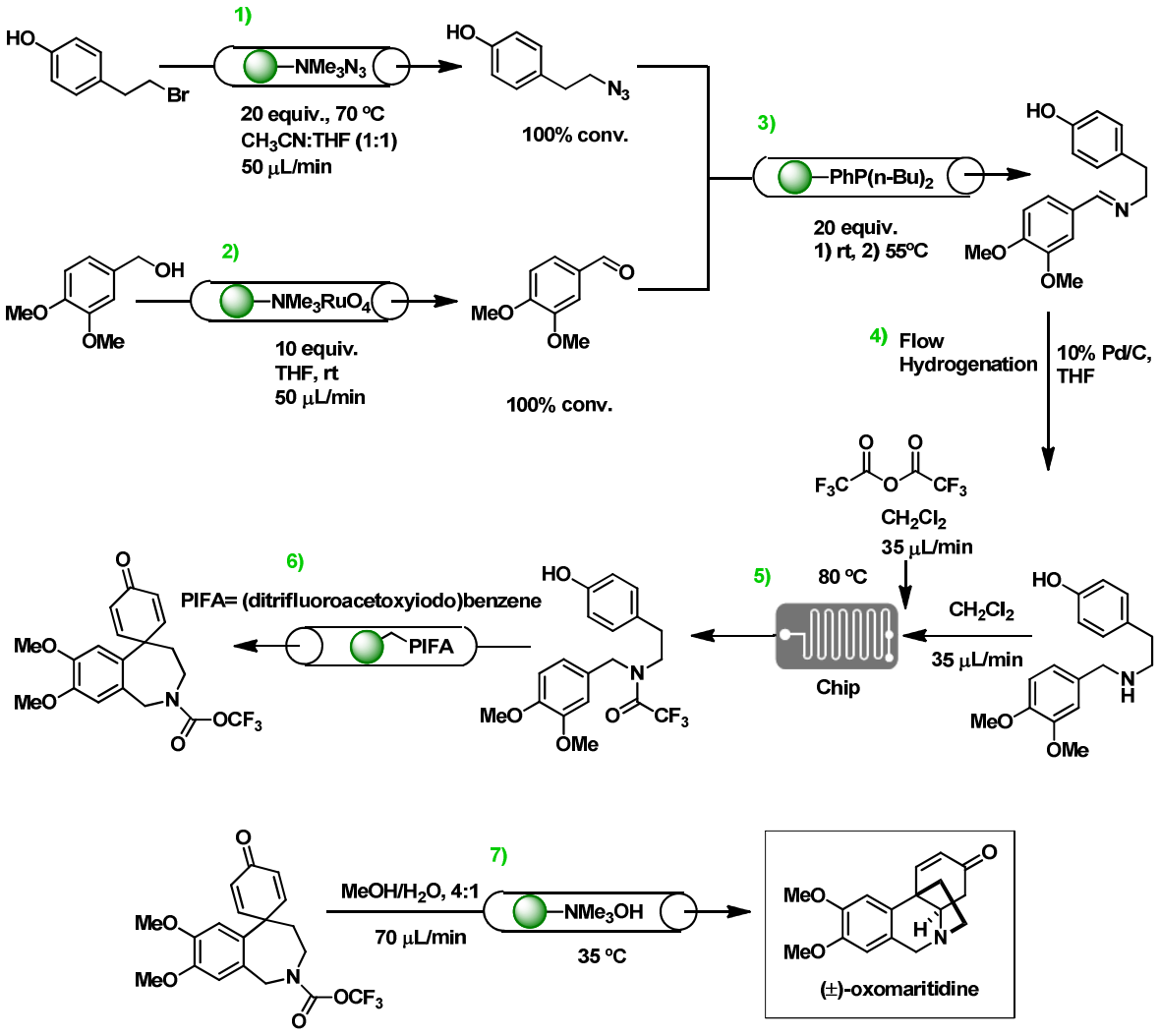


Figure 1.13. Multi-step synthesis strategies.

[65] a) Jas, G.; Kirschning, A. *Chem. Eur. J.* **2003**, *9*, 5708-5723. b) Kirschning, A.; Solodenko, W.; Mennecke, K. *Chem. Eur. J.* **2006**, *12*, 5972-5990. c) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300-2318. d) Wiles, C.; Watts, P. *Eur. J. Org. Chem.* **2008**, 1655-1671. e) Kirschning, A. *Beilstein J. Org. Chem.* **2009**, *5*, 15. f) Luis, S. V.; Garcia-Verdugo, E. *Chemical Reactions and Processes Under Flow Conditions, RSC, Cambridge*, **2010**. g) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583-4592.

[66] a) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675-680. b) Lévesque, F.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1706-1709.

Continuous flow multi-step synthesis has been applied to natural product synthesis by Ley *et al*. They completed the synthesis of the alkaloid natural product (±)-oxomaritidine by combining seven steps of synthesis into one continuous flow sequence. The product was obtained with over 90% purity, 40% overall isolated yield and the synthesis was accomplished in less than one day (Scheme 1.9).[67]



Scheme 1.9. Ley's synthesis of oxomaritidine in multi-step flow.

Due to its numerous benefits, continuous flow chemistry has also been studied in our research group, in both metal catalysis[60f,68] and organocatalytic[61e,g,l,j,m] applications. One of the privileged examples' in

[67] Baxendale, I. R.; Deeley, J.; Griffiths-Jones, C. M.; Ley, S. V.; Saaby S.; Tranmer, G. K. *Chem. Commun.* **2006**, *24*, 2566-2568.
[68] a) Pericàs, M. A.; Herrerías, C. I.; Solà, L. *Adv. Synth. Cat.* **2008**, *350*, 927-932. b) Rolland, J.; Cambeiro, X. C.; Rodríguez-Escrich, C.; Pericàs, M. A. *Belstein J. Org. Chem*. **2009**, *5*, 56. c) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Org. Lett*. **2012**, *14*, 1816-1819.

organocatalysis is the flow process for Mannich reaction, which involving a solid-supported catalyst allowed for the fast and enantiopure production of chiral products without purification.[61e] This constitutes the first application of a supported aminocatalyst in an enantioselective flow process.

1.4. OBJECTIVES

The present thesis deals mainly with the synthesis of homogeneous organocatalysts and their immobilization onto cross-linked polymeric resins. Following the general approach implemented by our group, it combines the optimization of the catalytic properties of the homogeneous ligands with the study of the solid supports. The developed anchored catalysts have been used in different carbon-carbon, and carbon-heteroatom bond forming reactions. Moreover, all the advantages of solid supported catalysts such as recycling, and continuous flow applications have been demonstrated with success on different examples. Therefore, we have been able to develop effective polymer-supported organocatalysts with high catalytic activities and enantioselectivities.

The general summary of this thesis by chapters is the following:

Chapter II will focus on the design and synthesis of polystyrene-supported, enantiopure (*S*)-α,α-diphenylprolinol ethers as recyclable organocatalysts for asymmetric Michael reactions. These immobilized organocatalysts have been evaluated in the reaction of aldehydes with nitroolefins via enamine activation and in the conjugated addition reaction of malonates to α,β-unsaturated aldehydes through iminium activation (**Paper A**).

Chapter III. Combining proline derived secondary amine with a thiourea scaffold a homogeneous bifunctional Bronsted base organocatalyst has been developed and used in the enantioselective *anti*-Mannich reaction. Newly designed pyrrolidine-based thiourea organocatalysts and the effect of the substitution pattern on the catalytic activity and the selectivity has been studied.

Chapter IV-I. This part of the work deals with the design and synthesis of polystyrene-supported H-bonding squaramide organocatalysts and their evaluation in the Michael addition of 1,3-dicarbonyl compounds to β-nitrostyrenes (**Paper B**). The use of the same catalyst in the Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes with very high enantioselectivities at low catalyst loadings and the demonstration of this PS-supported squaramide organocatalyst as a highly reactive and robust catalyst for continuous flow application has also been described (**Paper C**). ***Chapter IV-II*** describes the immobilization of a bifunctional H-bonding thiourea organocatalyst onto a cross-linked polystyrene

support. The catalytic activity has been evaluated in the α-amination reaction of 1,3-dicarbonyl compounds.

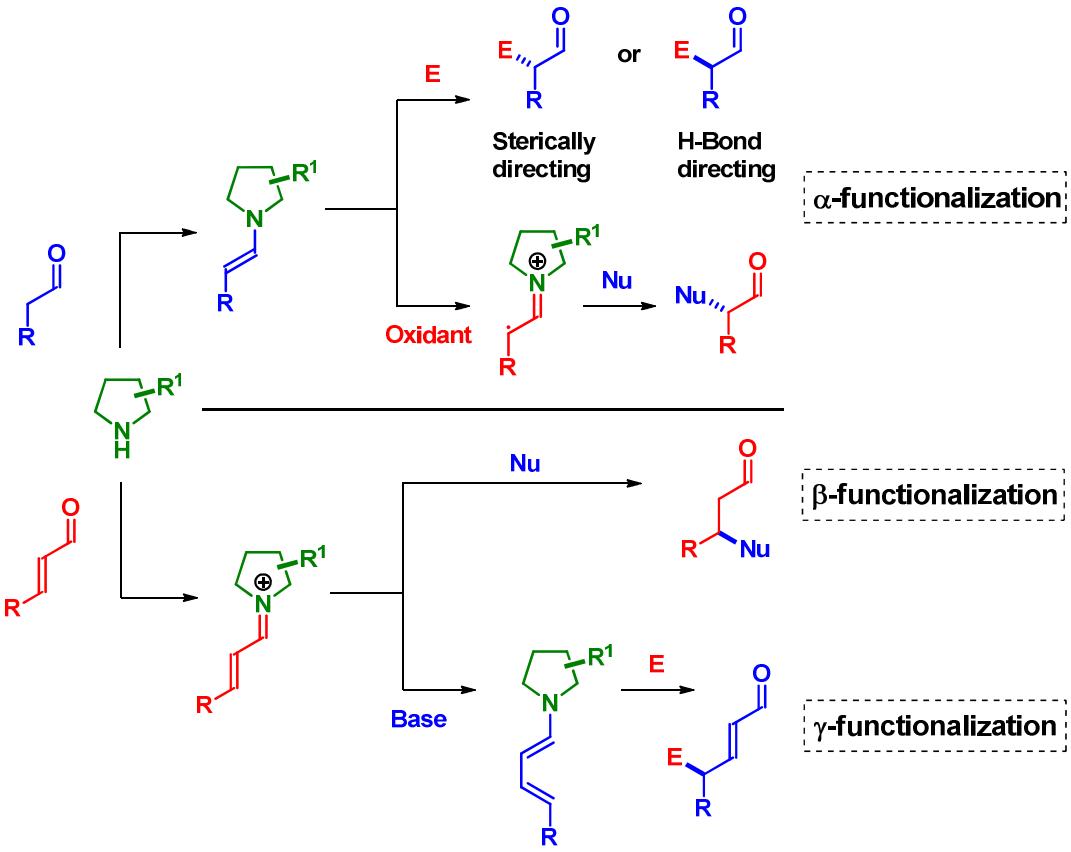
CHAPTER II

2. ENANTIOSELECTIVE PROLINOL ETHERS FOR ENAMINE AND IMINIUM ION ACTIVATION OF ALDEHYDES

2.1. ASYMMETRIC AMINOCATALYSIS

The term aminocatalysis refers to the use of substoichiometric amounts of chiral amines in the asymmetric functionalization of carbonyl compounds.[1] Although, the use of small organic molecules in organic transformations has been known before the introduction of organocatalysis concept, the use of secondary amines in the transformation of aldehydes is relatively new. In recent years, this concept has been successfully applied to several transformations and showed remarkable development. Reactions such as α, β, γ-functionalization of aldehydes and α,β-unsaturated aldehydes are the main examples of aminocatalysis. Remarkably, these can be combined in the so called cascade or tandem reactions to achieve the full potential of the concept. The main aminocatalytic pathways for carbonyl functionalization are shown in Scheme 2.1.

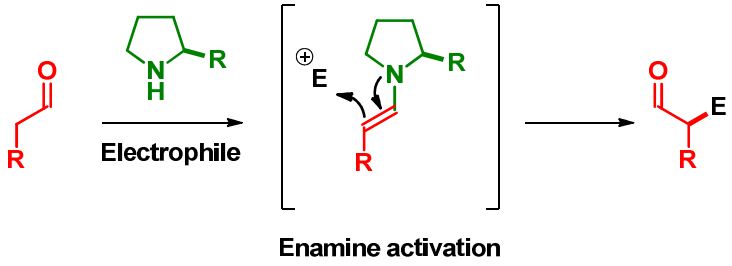
[1] a) List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc*. **2000**, *122*, 2395-2396. b) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243-4244. c) List, B. *Synlett* **2001**, *11*, 1675-1686. d) Movassaghi M.; Jacobsen, E. N. *Science* **2002**, *298*, 1904-1905. e) Dalko P. I.; Moisan, L. *Angew. Chem., Int. Ed*. **2004**, *43*, 5138-5175. f) Berkessel A.; Gröger, H. *Asymmetric Organocatalysis, VCH, Weinheim, Germany*, **2004**. g) Seayed J.; List B. *Org. Biomol. Chem*. **2005**, *3*, 719-724. h) List, B.; Yang, J. W. Science **2006**, *313*, 1584-1586. i) List, B. *Chem. Commun.* **2006**, *8*, 819-824. j) Marigo M.; Jørgensen, K. A. *Chem. Commun*. **2006**, *19*, 2001-2011. k) Guillena G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465-1492. l) Sulzer-Mossé S.; Alexakis, A. *Chem. Commun*. **2007**, *30*, 3123-3135. k) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569. m) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. C. *Drug Discovery Today* **2007**, *2*, 8-27. n) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, *11*, 1701-1716. o) Vicario, J. L.; Badía D.; Carrillo, L. *Synthesis* **2007**, *14*, 2065-2092. p) Almasi, D.; Alonso D. A.; Najera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299-365. q) Pellissier, H.; *Tetrahedron* **2007**, *63*, 9267-9331. r) Dalko, P. I. *Enantioselective Organocatalysis, Wiley-VCH, Weinheim*, **2007**. s) Dondoni A.; Massi, A. *Angew. Chem., Int. Ed*. **2008**, *47*, 4638-4660. t) Melchiorre, P.; Marigo, M.; Carlone A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138-6171. u). MacMillan, D. W. C *Nature* **2008**, *455*, 304-308. v) Bertelsen S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178-2189. w) Ueda, M.; Kano T.; Maruoka, K. *Org. Biomol. Chem.* **2009**, *7*, 2005-2012. x) Grondal, C.; Jeanty M.; Enders, D. *Nat. Chem*. **2010**, *2*, 167-178 y) Chen, X.-H.; Yu, J.; Gong, L.-Z. *Chem. Commun*. **2010**, *46*, 6437-6448. z) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun*. **2011**, *47*, 632-649.



Scheme 2.1. Aminocatalytic carbonyl functionalization pathways.[1z]

2.1.1. Enantioselective Aminocatalysis via Enamine

Activating the α-position of aldehydes and ketones to form carbon-carbon and carbon-heteroatom bonds via enamine formation is one of the most common and efficient mechanisms. Enamine intermediates are formed from the condensation of enolizable carbonyl compounds with secondary amine catalysts (Scheme 2.2), which generates a nucleophilic α-carbon (HOMO raising effect).[2]

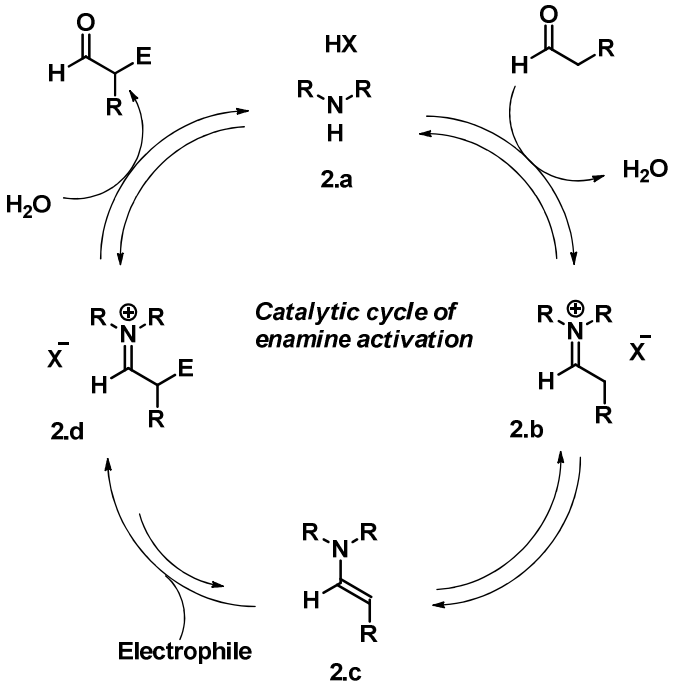


Scheme 2.2. Enamine activation mode.

[2] a) List, B. *Tetrehedron* **2002**, *58*, 5573-5590. b) List, B. *Acc. Chem. Res.* **2004**, *37*, 548-557. c) Mukherjee, S.; Woon, J.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471-5569. d) Tanaka, F.; Barbas III, C. F. *Enamine Catalysis in, Enantioselective Organocatalysis, Reactions and Experimental Procedures*, *ed. P. I. Dalko, Wiley-VCH, Weinheim*, **2007**.

There are two types of enamine catalysis described, depending on the class of electrophile used.[2b] If the double bond containing electrophiles are used formal insertion into the α-C-H bond of the carbonyl compound takes place via nucleophilic addition (such as aldehydes, imines, Michael acceptors, etc). If single bond electrophiles are used this formal insertion takes place via nucleophilic substitution as in the case of alkyl halides.

The general catalytic cycle of the enamine activation mode starts with the formation of iminium ion **2.b** by condensation of the carbonyl compound and the amine catalyst. Deprotonation of this species due to the increase in the acidity of the α-carbon generates the enamine **2.c**. This newly formed intermediate can react with different electrophiles by the increased energy of its HOMO orbital (in comparison to the enol form) thus forming, new carbon-carbon (C-C) or carbon-heteroatom (C-X) bonds (**2.d**). In the end, hydrolysis of the resulting iminium ion intermediate **2.d** forms the product and regenerates the amine catalyst **2.a** (Scheme 2.3).[3]



Scheme 2.3. General catalytic cycle of the enamine activation mode.

The enamine catalysts can be divided into two types according to the interaction between the enamine and the electrophile in the enantiodetermining step. One group of enamine catalysts control the approach of electrophile by

[3] Pihko, M. P.; Majander, I.; Erkkilä, A. *Top Curr Chem.* **2010**, *291*, 29-75.

hydrogen bonding assistance (Type A) and the other group of catalysts relies on steric bulk (Type B).[3] Type A catalysts include an internal acid/hydrogen bond donor group. Type B catalysts have bulky nonacidic groups (Figure 2.1).

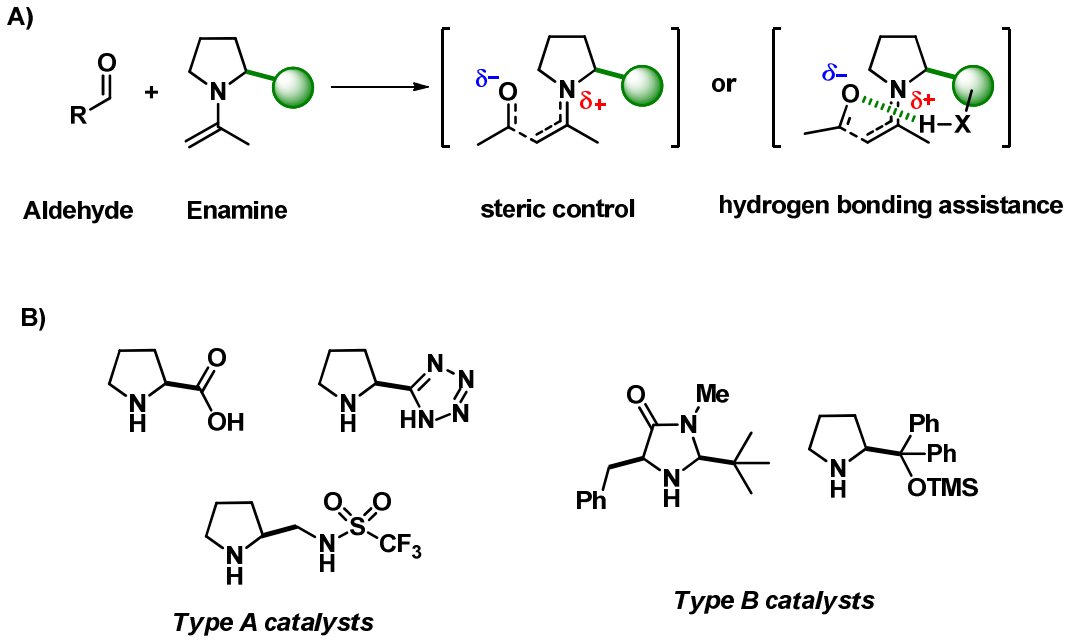
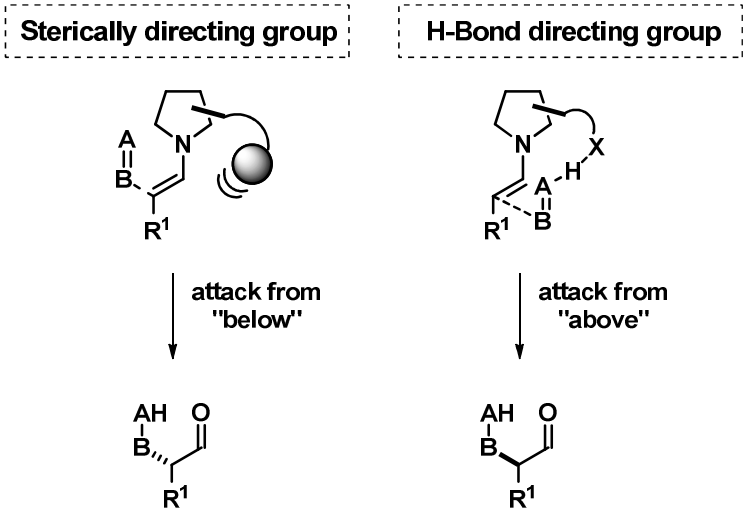


Figure 2.1. A) Enantioselectivity control by enamine catalysis. B) Selected examples of Type A and Type B catalysts.

The use of secondary amines as organocatalysts has found great application since the pioneering report of List, Lerner, and Barbas. They used the amino acid L-proline to promote the enantioselective direct aldol reaction between an unmodified ketone and variety of aldehydes.[1a] Afterwards, proline was used as a catalyst in many different reactions of ketones, aldehydes and enals. As it is explained before, using proline species it is assumed that the asymmetric induction is provided by the hydrogen bonding between the carboxylic acid of proline and the electrophile. However, in some cases proline catalysts proved to be inefficient to control asymmetric induction and new catalyst designs were needed. More or less in the same time interval than proline, MacMillan imidazolidinone catalysts were developed and shortly after, proline derived Hayashi-Jørgensen catalysts were used to control the stereoselectivity by sterical hindrance.

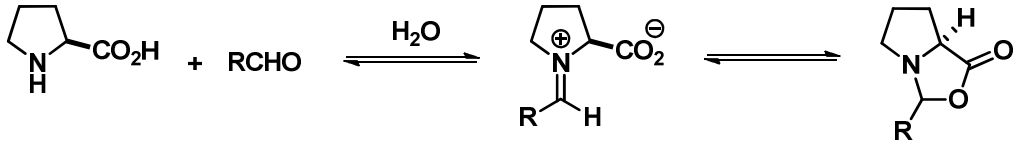
The L-proline catalyst belongs to the Type A group, which uses attractive hydrogen bonding interactions for the alignment and activation of substrates. By the help of carboxylic acid group, there is an interaction developed on the upper-

side of the catalyst, which directs the electrophile approach from this face. The second types of catalysts, like diphenylprolinols, rely on steric hindrance for face shielding and favor the approach of electrophiles from the opposite face[4] (Scheme 2.4).



Scheme 2.4. Different strategies to control the approach of the electrophile.

Although there are some earlier studies about the different species in proline catalyzed reaction mechanisms, in 2007, the activation mode of proline catalyst was explained in more detail by Seebach *et al.*[5] They postulated that in the stereochemical course of the reaction there is another species playing a key role. Instead of the carboxylic acid moiety, they proposed the assistance of an oxazolidinone species to promote the formation of enamine intermediate and electrophilic attack (Scheme 2.5).

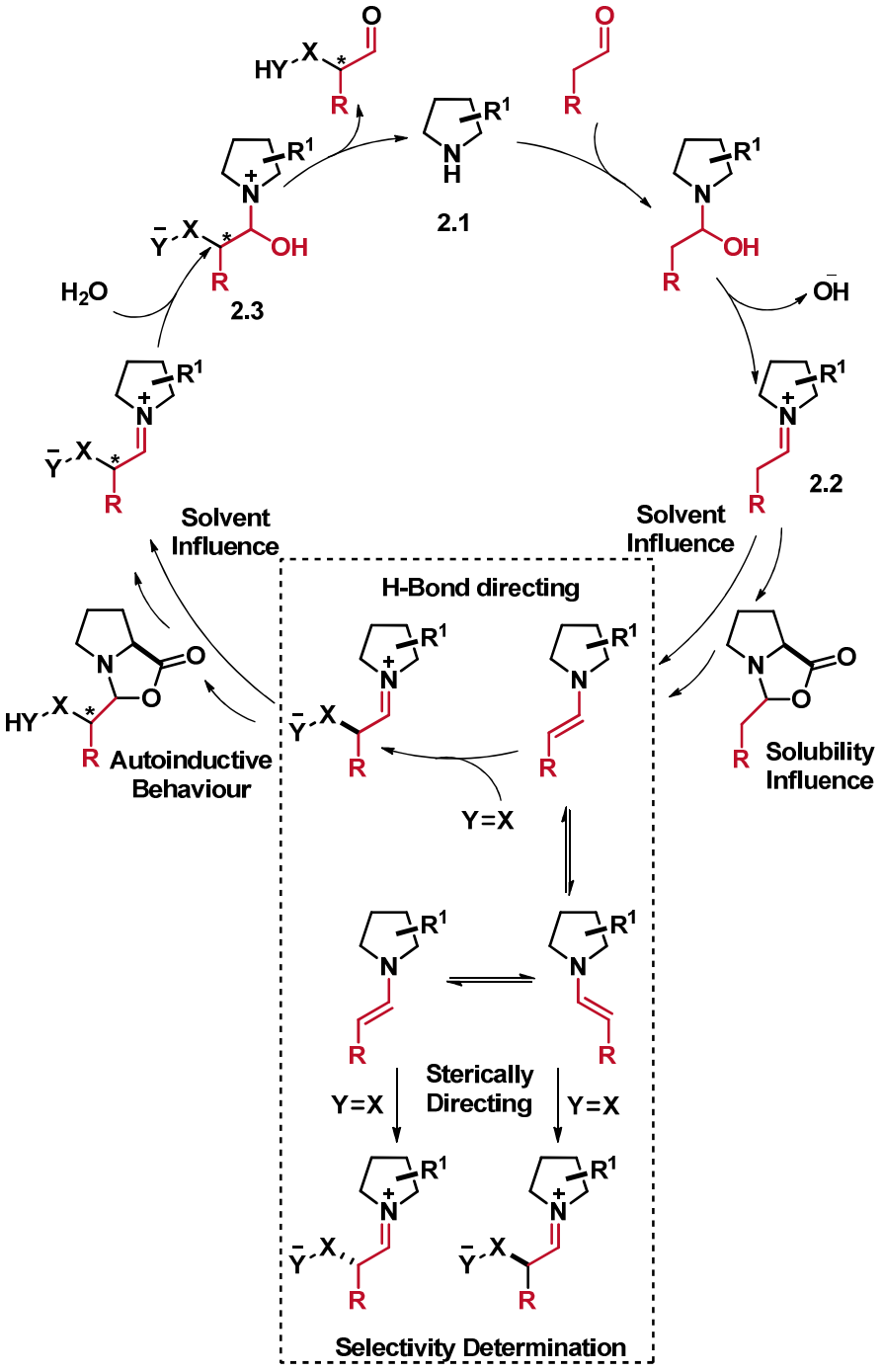


Scheme 2.5. Reversible formation of oxazolidinone from l-proline and aldehydes.

The published works highlight that, in enamine catalyzed reactions there should be more complicated intermediates than those in basically drawn catalytic

[4] Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc*. **2003**, *125*, 2475-2479.
[5] a) Iwamura, H.; Mathew, S. P.; Blackmond, D. G. *J. Am. Chem. Soc*. **2004**, *126*, 11770-11771. b) List, B.; Hoang, L.; Martin, H. J. *Proc. Natl. Acad. Sci.* **2004**, *101*, 5839-5842. c) Zotova, N.; Franzke, A.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc*. **2007**, *129*, 15100-15101. d) Seebach, D.; Beck, K. A.; Badine, D. M.; Limbach, M.; Eschenmoser, A.; Treasurywala, A. M.; Hobi, R.; Prikoszovich, W.; Linder, B. *Helv. Chim. Acta* **2007**, *90*, 425-471. e) Schmid, M. B.; Zeitler, K.; Gschwind, R. M. *Angew. Chem., Int. Ed*. **2010**, *49*, 4997-5003. g) Sharma, A. K.; Sunoj, R. B.; *Angew. Chem., Int. Ed*. **2010**, *49*, 6373-6377.

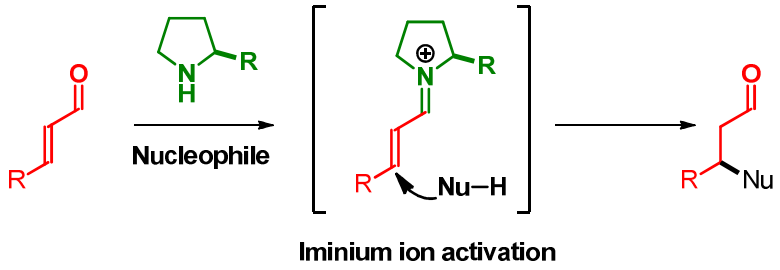
cycles.[1z] Jørgensen *et al.* have elucidated this catalytic cycle in more detail by considering different pathways (see Scheme 2.6).[1z] They explained that after the formation of iminium ion **2.2** from the hemiaminal, the aminocatalyst employed determines the approach of the incoming electrophile through either steric interactions (repulsion) or hydrogen bonding interactions (attractions). The last step, is the hydrolysis of the addition product **2.3** giving rise to the free catalyst **2.I** and α-functionalized aldehydes.



Scheme 2.6. Mechanistic scenario of α-functionalization for aldehydes with mechanistic details.

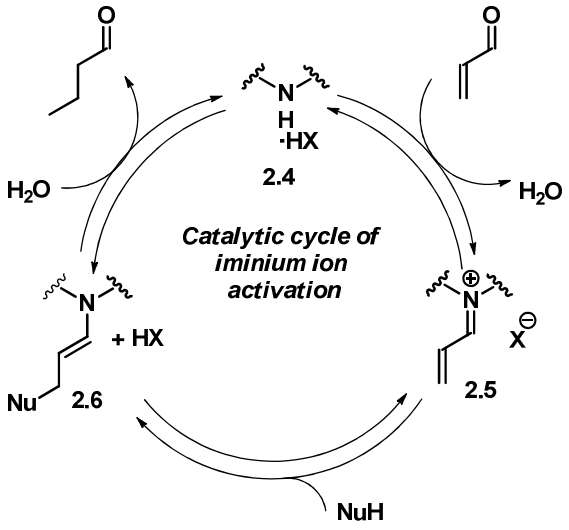
2.1.2. Enantioselective Aminocatalysis via Iminium Ion

Iminium ion activation is the other important activation strategy in aminocatalysis. This concept was introduced by MacMillan *et al.* in 2000.[1b] They performed the enantioselective Diels-Alder reaction between α,β-unsaturated aldehydes and different dienes. This iminium ion intermediate was obtained from the condensation of α,β-unsaturated aldehydes with an enantiopure aminocatalyst (Scheme 2.7). Formation of this iminium ion lowers the energy of the LUMO of the π-system and promotes the subsequent reactions.



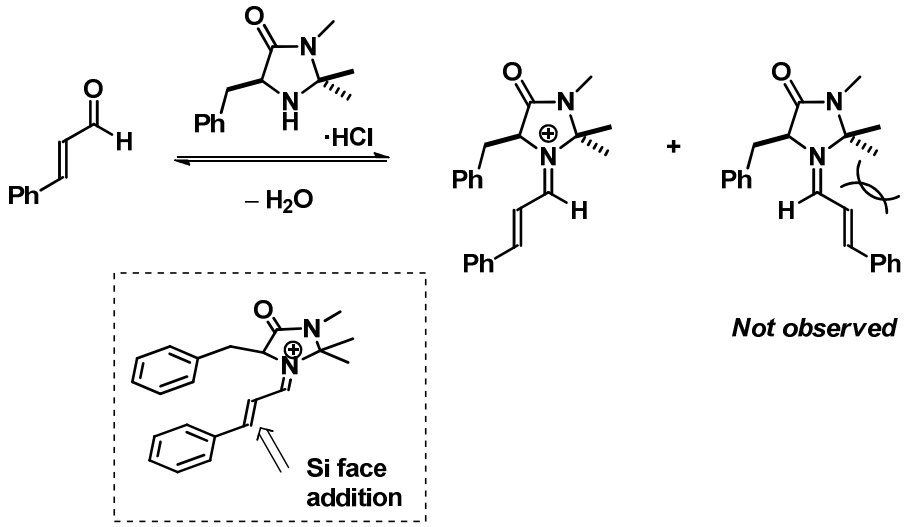
Scheme 2.7. Iminium ion activation mode of aminocatalysis.

The catalytic cycle of iminium ion catalysis start with the help of the co-acid (HX) used. The proton source facilitates both the formation and hydrolysis of iminium ion. First, reaction of the amine catalyst with the α,β-unsaturated carbonyl compound in the presence of acid co-catalyst forms iminium ion **2.5**. This newly formed intermediate **2.5** is more electrophilic than the starting enal (LUMO lowering) and can undergo attack by a nucleophile. Hydrolysis of the intermediate **2.6** forms the product and regenerates the active amine catalyst (Scheme 2.8).



Scheme 2.8. Catalytic cycle of iminium ion activation.

The iminium ion catalysts use bulky groups for the control of enantioselectivity as explained before, which categorizes then as Type B (Figure 2.1). In the initial report of MacMillan they used the imidazolidinonium salt catalyst to activate α,β-unsaturated carbonyl compounds towards cycloaddition.[1b] They observed single iminium ion formation from the condensation of aldehyde, which was explained with the disfavored steric interaction between the geminal dimethyl groups of the catalyst and α-carbon of the substrate (Scheme 2.9).



Scheme 2.9. Mode of action for imidazolidinone catalyst.

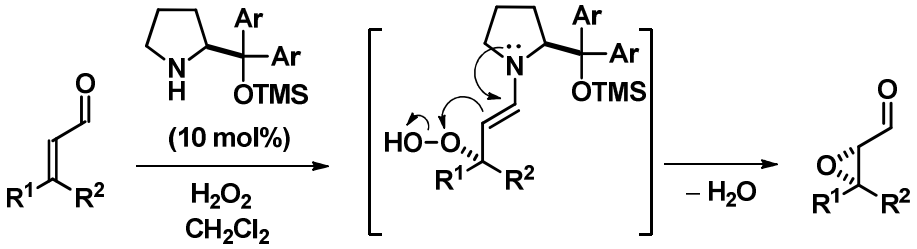
Diarylprolinol silyl ethers are another efficient family of catalysts used in iminium ion activation, with several applications in the literature in 1,4-addition reactions. The nucleophile scope is quite broad including several examples of hetero Michael addition reactions like oxa-, aza-, sulfa- and phospha- additions.[6] Besides the heteroatom examples, there are also carbon nucleophile additions,[7]

[6] a) Marigo,M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710-15711. b) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536-1537. c) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2007**, *46*, 1983-1987. d) Jiang, H.; Nielsen, J. B.; Nielsen, M.; Jørgensen, K. A. *Chem. Eur. J.* **2007**, *13*, 9068-9075. e) Maerten, E.; Cabrera, S.; Kjærsgaard, A.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 8893-8903. f) Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4504-4506.

[7] a) Brandau, S.; Landa, A.; Franzen, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2006**, *45*, 4305-4309. b) Franke, P. T.; Richter, B.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 6317-6321. c) Rueping, M.; Sugiono, E.; Merino, E. *Chem. Eur. J.* **2008**, *14*, 6329-6332. d) Cabrera, S.; Reyes, E.; Aleman, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2008**, *130*, 12031-12037. e) Hayashi, Y.; Obi, K.; Ohta, Y.;Okamura, D.; Ishikawa, H. *Chem.;Asian J.* **2009**, *4*, 246-249.

the first successful example being the malonate addition to α,β-unsaturated aldehydes reported by the Jørgensen group.[8]

One of the features that makes organocatalysis so powerful is that the abovementioned activation modes can be combined in one-pot operations by careful design of the reaction. For instance, diarylprolinol catalysts have proven to be very efficient for cascade reactions with sequential addition of nucleophiles and electrophiles, combining the iminium ion and enamine activation modes. It was demonstrated that in the epoxidation of α,β-unsaturated aldehydes with hydrogen peroxide, diphenyl prolinol catalyst first forms an iminium ion with the α,β-unsaturated aldehyde, which suffers the nucleophilic addition of peroxide to the β-carbon. The transiently generated nucleophilic enamine then attacks to the peroxide group, expelling water as the leaving group. Finally, hydrolysis of the iminium intermediate gives rise to the epoxy aldehyde (Scheme 2.10).[9]



Scheme 2.10. Aminocatalytic cascade reaction.

Apart from this epoxidation reaction, there are many examples in the literature using mainly diphenylprolinols as iminium ion/enamine catalysts in cascade reactions.[10]

2.2. TMS-DIARYLPROLINOL AND RELATED CATALYSTS

Due to the fact that this chapter deals with the use of this type of catalysts they will be discussed in more detailed in the following pages.

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[8] Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 18296-18304.
[9] Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964-6965.
[10] a) Brandau, S.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986-14991. b) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861-863. c) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed*. **2007**, *46*, 778-781. d) Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8468-8472. e) Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem. Eur. J.* **2010**, *16*, 1750-1753.

2.2.1. Enamine-, Dienamine- and Trienamine-Mediated Catalysis

After the ground-breaking work by List, Lerner and Barbas (enamine activation) and MacMillan (iminium ion activation), other aminocatalysts were developed to exploit these new concepts, as well as the related dienamine and trienamine activation pathways (Figure 2.2).[11]

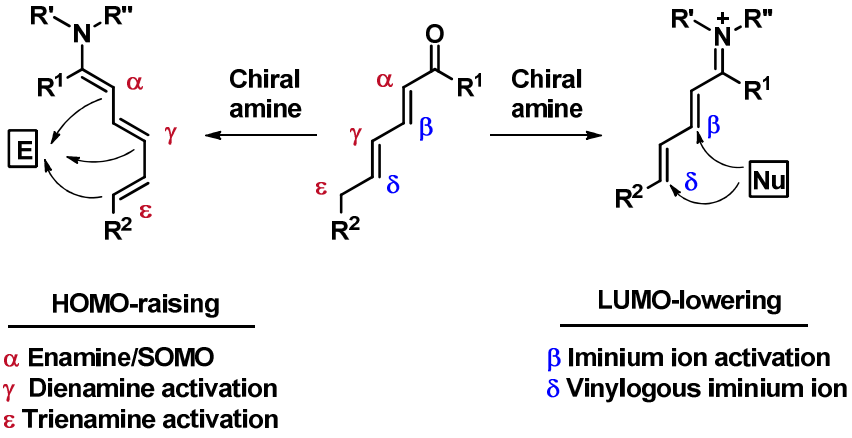

Figure 2.2. Vinylogous activation modes in aminocatalysis.[12]

Diarylmethylpyrrolidine and diarylprolinol catalysts were the privileged catalysts using other activation pathways after proline. The early examples of diarylmethylpyrrolidines reported in literature showed that the catalysts were insufficient in terms of providing good enantioselectivity.[13] The aryl groups on the catalyst cannot shield one face of the transient enamine or iminium ion properly, which affects the stereochemistry of the reaction. On the other hand, diarylprolinol provided higher stereocontrol, but it suffered low turnover due to the formation of stable and unreactive hemiaminal species.[14] To avoid this unreactive intermediate, the alcohol group was silylated. New designed diarylprolinol silyl ethers were highly reactive and provided high steric shielding and, consequently, good stereocontrol (Scheme 2.11).

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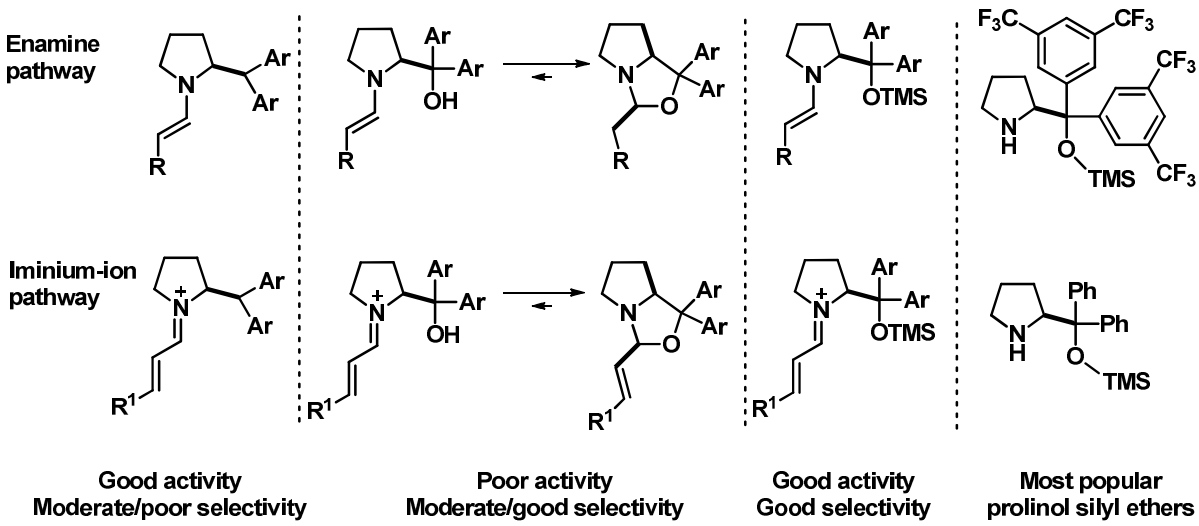
[11] Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, L.; Jørgensen, K. A. *Acc. Chem. Res*. **2012**, *45*, 248-264.
[12] Jurberg, I. D.; Chatterjee, I.; Tannert, R; Melchiorre, P. *Chem. Commun.* **2013**, *49*, 4869-4883.
[13] a) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151-4157. b) Juhl, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed*. **2003**, *42*, 1498-1501. c) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 794-797. d) Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2006**, *128*, 6804-6805. e) Ibrahem, I.; Santoro, S.; Himo, F.; Córdova, A. *Adv. Synth. Catal.* **2011**, *353*, 245-252.
[14] Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 18296-18304.

First the TMS-protected prolinol (TMS = Trimethylsilyl) catalyst was used for the α-sulfenylation of aldehydes by Jørgensen *et al.*[15] and in the Michael reaction of aldehydes and nitroalkenes by Hayashi *et al*.[16] Shortly after, in 2006, the Jørgensen group extended the scope of enamine mediated reactions by successfully combining the electron conjugation system in α,β-unsaturated carbonyl compounds with HOMO raising activity of TMS-protected diarylprolinol. This new concept provided the γ-functionalization of α,β-unsaturated aldehydes by dienamine activation (Figure 2.2).[12,17] However, due to the difficult site selectivity control in the formed dienamine species, it is hard to achieve direct functionalization at γ-position, and it has found more use in cycloaddition reactions.[18]



Scheme 2.11. Catalyst structures and modes of stereoinduction.

Therefore, some new catalysts were designed such as bifunctional secondary amine thioureas, to activate the electrophile by hydrogen bonding, while activating the unsaturated aldehyde as a dienamine. In this line, the Jørgensen group has designed new bifunctional secondary amine squaramide

[15] Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2005**, *44*, 794-797.
[16] Hayashi, Y.; Gotoh, H; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed*. **2005**, *44*, 4212-4215.
[17] Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2006**, *128*, 12973-12980.
[18] a) de Figueiredo, R. M.; Fröhlich, R.; Christmann, M. *Angew. Chem., Int. Ed*. **2008**, *47*, 1450-1453. b) Duarte, F. J. S.; Santos, A. G. *J. Org. Chem*. **2012**, *77*, 3252-3261. c) Orue, A.; Reyes, E.; Vicario, J. L.; Carrillo, L.; Uria, U. *Org. Lett.* **2012**, *14*, 3740-3743.

organocatalysts for the γ-site selective functionalization of enals.[19] They performed the formal [2+2] cycloaddition reaction of dienamines with nitroolefins to form cyclobutanes with high yields and excellent enantio- and diastereoselectivities. These bifunctional catalysts and cooperative dienamine/hydrogen-bonding catalysts have also been used in some other cycloaddition reactions efficiently.[20]

Furthermore, the HOMO raising concept can be extended to the trienamine activation (Figure 2.2), first demonstrated in 2011 by Jørgensen *et al.* in Diels-Alder and tandem reactions.[21] By the help of trienamine activation it is possible to form new C-C bonds at the β and ε positions of the conjugated enals or enones, transferring stereochemical information to this position located at six atoms distance from the stereocenter. In short time, this activation concept has started to be successfully used by many other research groups with the TMS-protected prolinol catalyst or with different catalysts.[22]

2.2.2. TMS-Diarylprolinol Catalyzed 1,4-Michael Addition to α,β-Unsaturated Aldehydes

The conjugate addition reaction, which is simply described as the addition of nucleophiles to electron poor alkenes, is one of the most versatile C-C and C-heteroatom bond forming reaction.[23] Asymmetric catalysts have been widely used in Michael addition reactions and also organocatalysts have shown spectacular reactivity and selectivity. As we have mentioned before, the TMS-diarylprolinol system is one of the privileged organocatalysts that promotes conjugate addition reactions efficiently. The first carbon nucleophile addition to α,β-unsaturated aldehydes mediated by a TMS-diarylprolinol catalyst (**2.7**) was reported in 2006 by

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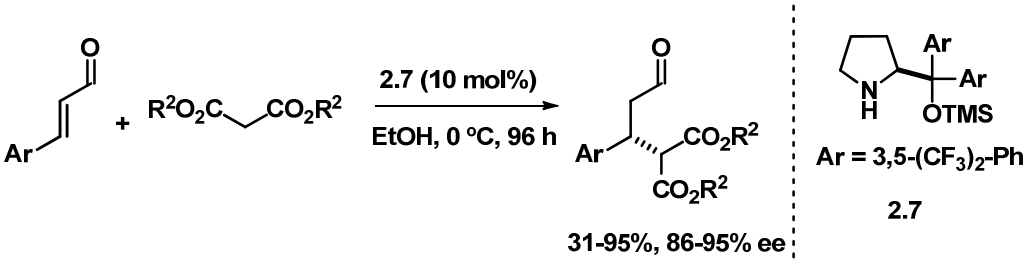
[19] Albrecht, Ł.; Dickmeiss, G.; Acosta, F. C.; Rodríguez-Escrich, C.; Davis R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2012**, *134*, 2543-2546.
[20] a) Albrecht, Ł.; Dickmeiss, G.; Weise, C. F., Rodríguez-Escrich C.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 13109-13113. b) Talavera, G.; Reyes, E.; Vicario J. L.; Carrillo, L. *Angew. Chem., Int., Ed.* **2012**, *51*, 4104-4107.
[21] Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2011**, *133*, 5053-5061.
[22] a) Jiang, H.; Gschwend, B.; Albrecht, Ł.; Hansen, S. G.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 9032-9036. b) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638-8641. c) Liu, Y.-K.; Nappi, M.; Arceo, E.; Vera S.; Melchiorre, P. *J. Am. Chem. Soc*. **2011**, *133*, 15212-15218. d) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310-1313. e) Ma, C.; Jia, Z.-J.; Liu, J.-X.; Zhou, Q.-Q.; Dong L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2013**, *52*, 948-951. f) Zhang, S.-J.; Zhang, J.; Zhou, Q.-Q.; Dong, L.; Chen, Y.-C. *Org. Lett.* **2013**, *15*, 968-971. g) Jiang, H.; Cruz Cruz, D.; Li, Y.; Lauridsen, V. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 5200-5207.
[23] Perlmutter, A. *Conjugate Additions in Organic Synthesis*, *Pergamon Press, Oxford,* **1992**.

Jørgensen *et al.*[24] They developed the enantioselective addition of malonates to aromatic α,β-unsaturated aldehydes with good yields and enantioselectivities; however reaction times were too long (Scheme 2.12).



Scheme 2.12. TMS-Diarylprolinol catalyzed Michael additions of malonates to enals.

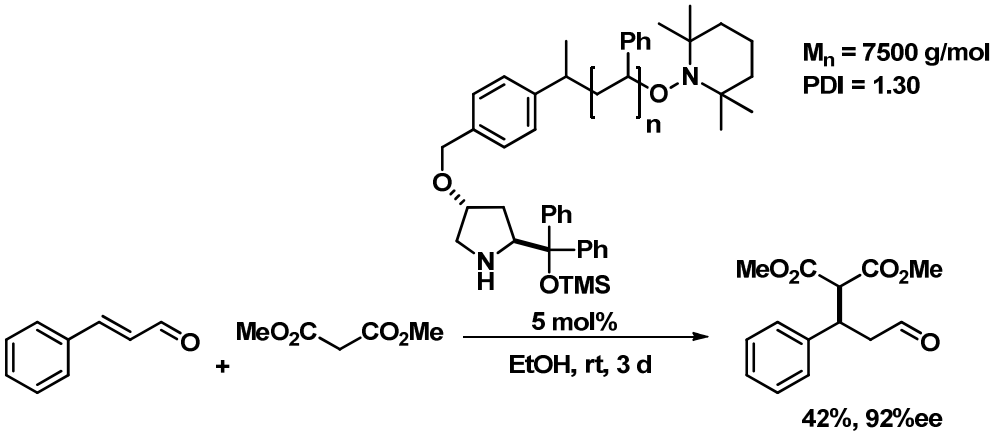
Thereafter Ma *et al.* developed the Michael addition of malonates to α,β-unsaturated aldehydes catalyzed by TMS-diarylprolinols in the presence of acetic acid and in aqueous media.[25] They extended the scope of the reaction to alkyl- and alkenyl-substituted enals and also they improved significantly the reaction times. They correlated the higher ee's, yields and shorter reactions times with the use of Brønsted acid and water as reaction medium. In 2008, Ye *et al.* developed Lewis base–Brønsted base bifunctional catalysts for the same reaction, using TMS-diarylprolinols as a Lewis base to activate α,β-unsaturated compound through iminium ion formation.[26] At the same time they used a basic lithium salt as a Brønsted base to activate the nucleophile by deprotonation. They showed the effect of base on the reaction by obtaining high yields and ee's in shorter reaction times.

2.2.3. Immobilized Diarylprolinols

Due to their high reactivity, selectivity and stability TMS-diarylprolinol catalysts, have also found use in heterogeneous catalytic systems. The group of Studer synthesized prolinol-oligostyrene conjugates and then immobilized them onto a polystyrene matrix[27] to obtain a fibrous catalytic system. However, the chemical yield obtained from the reaction of dimethyl malonate with cinnamaldehyde was lower when compared to its homogeneous counterpart.

[24] Brandau, S.; Landa, A.; Franzen, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305-4309.
[25] Ma, A.; Zhu, S.; Ma, D. *Tetrahedron Lett.* **2008**, *49*, 3075-3077.
[26] Wang, Y.; Li, P.; Liang, X.; Ye, J. *Adv. Synth. Catal.* **2008**, *350*, 1383-1389.
[27] Röben, C.; Stasiak, M.; Janza, B.; Greiner, A.; Wendorff, J. H.; Studer, A. *Synthesis* **2008**,*14*, 2163-2168.

Besides, in the recycling experiments, the fiber catalyst started to show much lower reactivity after the third run (Scheme 2.13). The same catalyst has been immobilized on to MeOPEG (methoxy poly(ethylene glycol)) support by Zeitler *et al.* and used successfully in the nitromethane addition to α,β-unsaturated aldehydes.[28] In that case, the supported catalyst worked very similar to its homogeneous counterpart, with high yields and enantioselectivities recorded. In the recycling experiments they observed decrease of yield after the fifth cycle.



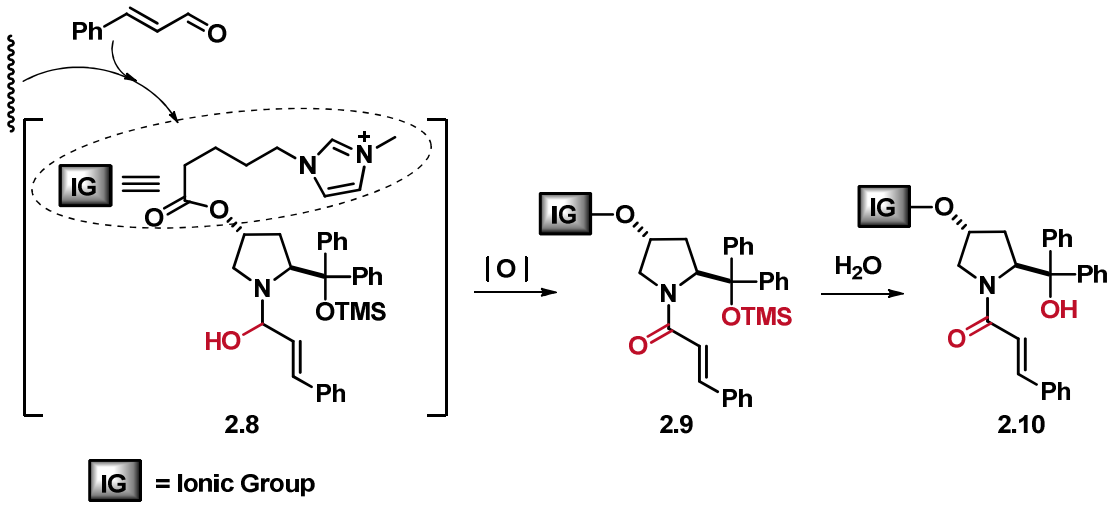
Scheme 2.13. Michael addition of dimethyl malonate to cinnamaldehyde with fibrous TMS-prolinol catalyst.

The previous works done by several research groups, including our own, and the experience we have acquired show that supported TMS-diarylprolinol catalysts suffer from deactivation problems in long time use or in the recycling. The loss of catalytic activity is commonly associated with the desilylation of the catalyst and formation of stable, unreactive cyclic hemiaminal species from the free prolinol.[29] In most cases, catalysts were treated with silylating agents (Me_3SiOTf or $Me_2NCOOSiMe_3$) after the deactivation period to recover the activity.[29]

However, the loss of the silyl group is not the only possible deactivation pathway. In 2011, Zlotin *et al.* published a study on deleterious side reactions that lower the catalytic efficiency of the TMS-diarylprolinol catalyst.[30] They performed a study with electron spray ionization mass spectroscopy (ESI-MS) by detecting the

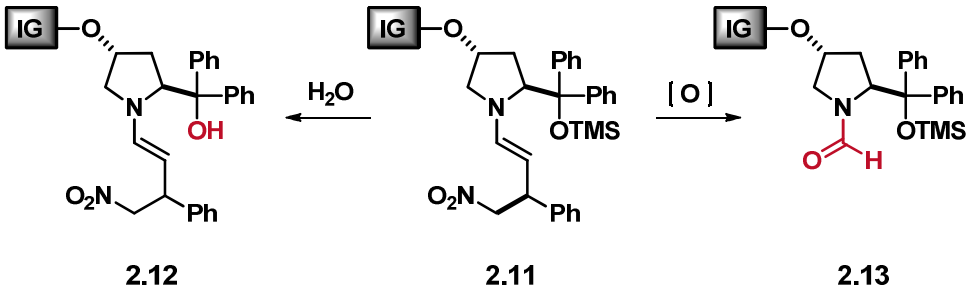
[28] Mager, I.; Zeitler, K. *Org. Lett.* **2010**, *12*, 1480-1483.
[29] a) Varela, M. C.; Dixon, S. M.; Lamb, K. S.; Schore, N. E. *Tetrahedron* **2008**, *64*, 10087-10090. b) Alza, E.; Pericàs, M. A. *Adv. Synth. Catal*. **2009**, *351*, 3051-3056.
[30] Maltsev, O. V.; Chizhov, A. O.; Zlotin, S. G. *Chem. Eur. J.* **2011**, *17*, 6109-6117.

ionic species present in the reaction media. TMS-diarylprolinol catalyst was used with an ionic group on C4 position in the reaction of nitromethane addition to cinnamaldehyde. In this manner, they detected the formation of hemiaminal species **2.8** and this intermediate can react with nucleophiles or oxidizing agents (for instance, the oxygen in the air). Alternatively, it may give oxidation side products **2.9** or the desilylation product **2.10** (Scheme 2.14). Also detected enamine intermediate **2.11** could undergo hydrolysis to give **2.12** (OH-catalyst) and oxidation side product **2.13** (inactive *N*-formyl pyrrolidine catalyst) (Scheme 2.15).



Scheme 2.14. ESI-MS detected intermediates in the reaction of nitromethane addition to cinnamaldehyde.

As a conclusion, they explained that hydrolysis and oxidation reactions take place under ambient atmosphere, and if reactions are conducted under inert atmosphere the catalytic activity of the TMS-diarylprolinol is retained for longer time.



Scheme 2.15. ESI-MS detected hydrolysis **2.12** intermediate and oxidation side product **2.13**.

In this chapter we will focus on the design and synthesis of polystyrene-supported, enantiopure (*S*)-α,α-diphenylprolinol ethers as recyclable

organocatalysts for asymmetric Michael reactions. These immobilized organocatalysts have been evaluated in the reaction of aldehyde with nitroolefins via enamine activation and in the conjugated addition reaction of malonates to α,β-unsaturated aldehydes through iminium activation.

Paper A

Polystyrene-Supported Diarylprolinol Ethers as Highly Efficient Organocatalysts for Michael-Type reactions

Chem. Eur. J. **2011**, *17*, 11585 – 11595

Esther Alza, Sonia Sayalero, Pinar Kasaplar, Diana Almasi, and Miquel A. Pericàs

Paper A – The works with polystyrene-supported (*S*)-α,α-diphenylprolinol trimethylsilyl ether were done by Esther Alza.

FULL PAPER

DOI: 10.1002/chem.201101730

Polystyrene-Supported Diarylprolinol Ethers as Highly Efficient Organocatalysts for Michael-Type Reactions

Esther Alza,[a] Sonia Sayalero,[a] Pinar Kasaplar,[a] Diana Almaşi,[a] and Miquel A. Pericàs*[a, b]

Abstract: α,α-Diphenylprolinol methyl- and trimethylsilyl ethers anchored onto a polystyrene resin have been prepared by a copper-catalyzed azide–alkyne cycloadditions (CuAAC). The catalytic activity and enantioselectivity displayed by the *O*-trimethylsilyl derivative are comparable to those exhibited by the best known homogeneous catalysts for the addition of aldehydes to nitroolefins and of malonates or nitromethane to α,β-unsaturated aldehydes. The combination of the catalytic unit, the triazole linker, and the polymeric matrix provides unprecedented substrate selectivity, in favor of linear, short-chain aldehydes, when the organocatalyzed reaction proceeds by an enamine mechanism. High versatility is noted in reactions that proceed via an iminium ion intermediate. The catalytic behavior of polystyrene-supported α,α-diphenylprolinol methyl ether was also evaluated in asymmetric Michael addition reactions. As a general trend, the CuAAC immobilization of diarylprolinol ethers onto insoluble polystyrene resins offers important operational advantages, such as high catalytic activity, easy recovery from the reaction mixture by simple filtration, and the possibility of extended reuse.

Keywords: aldehydes · asymmetric catalysis · Michael addition · organocatalysis · solid-phase catalysts

Introduction

The covalent immobilization of chiral catalytic species onto polymer supports has become an important research area over the last decade,[1] mainly due to the inherent properties of the polymer backbone, which allows easy recovery by simple filtration, recycling, reuse, and even application in continuous-flow processes. However, this strategy sometimes leads to a decrease in catalytic activity with respect to the monomeric species because of a deficient interaction between the reactants and the supported catalyst. This is accompanied by a decrease in enantioselectivity due to perturbation of the transition state of the enantiodetermining step by the polymer chain. Thus, appropriate design and preparation of the heterogeneous catalytic systems is essential to achieve catalytic activities and selectivities comparable to those provided by their homogeneous counterparts. Besides proper selection of the position on the homogeneous catalyst to be modified to create an anchoring point, the nature of the linker, spacer (if any), and polymer support plays also a fundamental role in determining the catalytic activity and stereoselectivity of the supported species. The more widely used supports that allow homogeneous conditions to be closely approached are highly swellable, yet insoluble, resins made of slightly cross-linked polystyrene-based polymers. Such polymers are readily available, can be easily functionalized by various methods, and have high chemical inertness.[2] Among them, Merrifield resins and their derivatives are ideal carriers for catalytic species due to their easy handling, optimal physical properties, and modularity.[3]

The continued and ever-growing interest in organocatalysis over the past two decades has led to the development of many different types of organocatalyzed reactions that provide enantiomerically pure compounds through very simple reaction setups.[4] However, many of these reactions lead to rather polar products, so isolation and purification become the main sources of solvent consumption and waste generation. Taking into account factors such as separation, catalyst recovery, and ease of purification of the reaction products, the immobilization of organocatalytic species appears a promising strategy.

In a continued effort towards the development of chemical processes with improved sustainability characteristics, we have introduced a variety of organocatalysts synthesized from pyrrolidine derivatives and anchored onto insoluble polystyrene resins[5a–g] by copper-catalyzed azide–alkyne cycloaddition (CuAAC).[6] The nature of the catalytic species, the presence of the triazole linker, and the environment pro-

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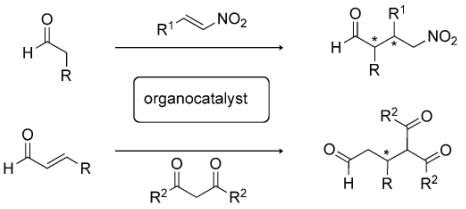
vided by the polymer backbone have shown a synergistic effect, which has led to remarkably high catalytic activity and enantioselectivity.[5a–g]

Catalysis mediated by primary or secondary amines include reactions that take place via enamine and iminium ion intermediates.[7] Among these processes, Michael reactions[8] represent a powerful synthetic tool for the assembly of 1,5-difunctionalized compounds (Scheme 1). Within the wide



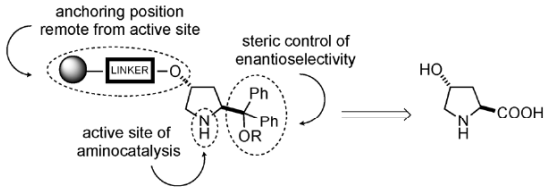
Scheme 1. Michael reaction of aldehydes with nitroolefins and malonates via enamine and iminium ion intermediates, respectively.

application range of these chemical transformations, their use as the first step in cascade processes,[9] or use of a combination of the two catalysis mechanisms in tandem sequences, has aroused a great deal of interest because complex molecular frameworks can be constructed in simple, one-pot operations. Of particular interest are catalysts derived from (*S*)-α,α-diarylprolinol silyl ethers,[10] independently introduced by Jørgensen and Hayashi for the enantioselective organocatalyzed α-sulfenylation of aldehydes and asymmetric Michael addition of aldehydes to nitroalkenes, respectively.[11] The steric effect caused by the bulky substituent placed at C2 on the pyrrolidine ring controls the enantioselectivity of the reactions very efficiently.

We have recently reported[5f] the development of a new immobilized, enantiopure (*S*)-α,α-diphenylprolinol trimethylsilyl ether (**4**)—supported onto polystyrene by a CuAAC reaction—that displays an unprecedented selectivity in favor of linear, short-chain aldehyde donors in the highly enantioselective Michael addition to nitroolefins. The same strategy was subsequently employed by Mager and Zeitler for the attachment of the same monomer to soluble methoxy polyethyleneglycol polymers.[5h] Herein, we report a full account of the design and synthesis of **4**, the chemical modification of this species as a methyl ether to obtain an extended life cycle, and the use of these catalysts in a variety of Michael reactions with aldehyde, malonate, or nitromethane donors and nitroolefin or α,β-unsaturated aldehyde acceptors.

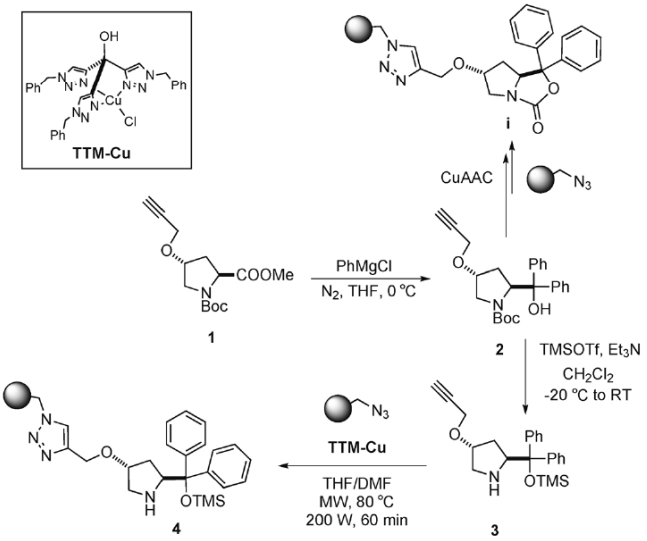
Results and Discussion

Design and synthesis of polystyrene-supported (*S*)-α,α-diphenylprolinol trimethylsilyl ether (4) and its evaluation in the Michael addition of aldehydes to nitroolefins: The asymmetric organocatalytic Michael addition[12] has emerged as one of the most important carbon–carbon bond-forming reactions and aldehydes have proven to be very reactive and convenient donors in this process. Catalysts derived from (*S*)-α,α-diarylprolinol silyl ethers have provided excellent results in terms of activity and selectivity for aminocatalytic enantioselective Michael reactions. For the design of a widely applicable polymer-supported Jørgensen–Hayashi-type organocatalyst, we reasoned that the immobilization strategy should involve the functionalization of these systems at the most remote position from the catalytic active amine moiety and the chiral C2 atom, to avoid perturbation of the enantiodetermining transition state by the linker and the polymeric backbone (Scheme 2).



Scheme 2. Supported organocatalyst design.

We selected natural hydroxyproline as our starting material and a CuAAC reaction as the covalent strategy to anchor the pyrrolidine moiety onto Merrifield resin (Scheme 3). This well-established atom-economic immobilization approach[5] required some synthetic effort to prepare the key intermediate **3** from the propargyloxy derivative (**1**) of commercially available *N*-Boc-(2*S*,4*R*)-4-hydroxyproline methyl ester (Boc = *tert*-butoxycarbonyl). The silylation, with concomitant carbamate deprotection of **2**, afforded the desired intermediate **3**,[5f] ready to be attached to the support by the selected methodology. The CuAAC reaction planned for the



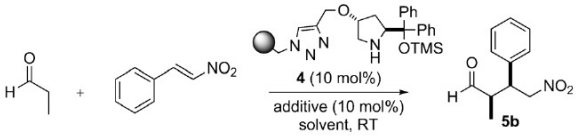
Scheme 3. Immobilization reaction to obtain polystyrene-supported (*S*)-α,α-diphenylprolinol trimethylsilyl ether (**4**).

conjugation step represented an important synthetic challenge because common Cu^{I} catalysts employed for the cycloaddition were incompatible with the free amino group present in the substrate. Notably, the immobilization of **3** onto azidomethylpolystyrene was efficiently catalyzed by the tris(triazolyl)methanol–copper complex (**TTM-Cu**),[13] which allowed the easy and highly reproducible synthesis of the catalytic resin **4**.

Notably, when the immobilization was performed at an earlier stage (immobilization of **2** to give resin **i**) the unavoidable formation of a cyclic carbamate was observed. Hydrolysis of this class of intermediates is feasible in homogeneous phase, however, it posed severe experimental difficulties on polymer substrates.

Recently, significant progress in the development of the organocatalytic Michael reaction has been achieved through the introduction of a variety of catalytic species and reaction conditions. These include reaction in aqueous media or in less-conventional environments, such as ionic liquids.[14] In this context, the Michael addition of propionaldehyde to β-nitrostyrene was selected as a model reaction for optimization of the reaction conditions with **4** as a catalyst (Table 1).

Table 1. Screening of reaction conditions for the Michael addition of propionaldehyde to (*E*)-β-nitrostyrene.[a]



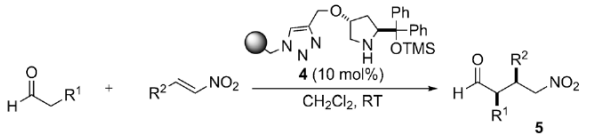
	Solvent	Additive[b]	*t* [h]	Conv [%][c]	*syn*/*anti*[c]	*ee* [%][d]
1[e]	hexane/THF	none	36	40	97:3	97
2[e]	CH_2Cl_2	none	7	>99	96:4	>99
3[e]	CH_2Cl_2	DMAP	24	>99	81:19	99
4[e]	CH_2Cl_2	PhCOOH	24	>99	77:23	97
5	CH_2Cl_2	none	7	>99	>99:1	>99
6	CH_2Cl_2	DMAP	23	>99	86:14	>99
7	CH_2Cl_2	PhCOOH	2	>99	87:13	99
8	H_2O	diMePEG	24	97	96:4	99
9	CH_2Cl_2	TFA	48	none	–	–

[a] General conditions: (*E*)-β-nitrostyrene (0.2 mmol), propionaldehyde (0.3 mmol), and **4** (0.02 mmol), solvent (1 mL), RT. [b] Additive (0.02 mmol). [c] Conversion determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Propionaldehyde (2 mmol).

It was established that CH_2Cl_2 was the optimal solvent for the reaction. Although different additives were tested (Table 1, entries 3, 4, 6–8), optimal results were recorded with the use of 10 mol% catalyst in the absence of any additive (Table 1, entry 5). Notably, these optimal conditions involve the use of a 1.5:1.0 molar ratio of aldehyde/nitrostyrene, much more convenient than the usually employed 10:1 ratio. Indeed, Michael adducts were obtained in this manner with better diastereoselectivity and from cleaner crude reaction products due to the suppression of aldehyde self-condensation reactions. When volatile substrates were used, the direct isolation of the pure products was possible by simple filtration of the catalyst and evaporation of the solvent. In any case, it is also important to emphasize the excellent performance of **4** in water; this reaction is the first example of an insoluble organocatalyst successfully promoting reaction with aldehydes in an aqueous medium.[5c]

The scope of the Michael addition between aldehydes and nitroolefins mediated by **4** was next studied. The results are presented in Table 2. As a general trend, the *syn* Michael

Table 2. Screening of substrates in the Michael addition of aldehydes to nitroolefins catalyzed by **4**.[a]



	R^1	R^2	**5**	*t* [h]	Conv[b] [%]	Yield[c] [%]	d.r.[b]	*ee*[d] [%]
1	H	Ph	**5a**	72	50	44	–	96
2	Me	Ph	**5b**	7	>99	98	>99:1	>99
3	Et	Ph	**5c**	5	>99	93	90:10	>99
4	Pr	Ph	**5d**	27	>99	98	82:18	99
5	n-pent	Ph	**5e**	48	99	91	75:25	98
6	*i*Pr	Ph	**5f**	96	<10	–	n.d.[e]	n.d.
7	Ph	Ph	**5g**	48	<5	–	n.d.	n.d.
8	$(CH_3)_2$	Ph	**5h**	120	0	–	n.d.	n.d.
9	Me	4-BrC_6H_4	**5i**	4	>99	98	91:9	98
10	Me	4-$MeOC_6H_4$	**5j**	8	>99	94	89:11	99
11	Me	2-furyl	**5k**	4	>99	96	85:15	90
12	Me	$(CH_2)_2C_6H_5$	**5l**	24	>99	94	81:19	95
13	Me	C_6H_{11}	**5m**	64	>99	89	70:30	97
14	Me	*i*Pr	**5n**	96	88	84	70:30	99

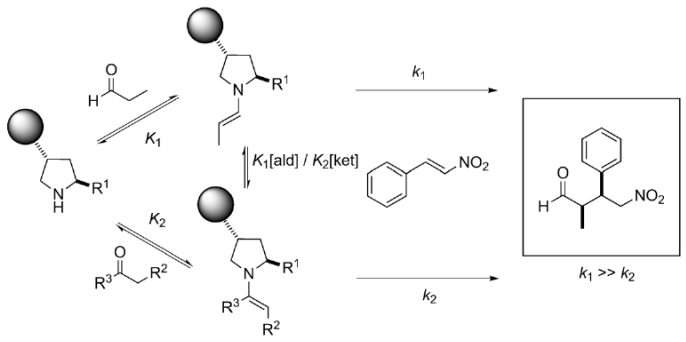
[a] General conditions: nitroolefin (0.2 mmol), aldehyde (0.3 mmol), **4** (0.02 mmol), solvent (1 mL), RT. [b] Conversion and diastereomeric ratio (d.r.) determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] n.d. = not determined.

products **5** were obtained with excellent diastereo- and enantioselectivity. Even in the challenging Michael reaction of acetaldehyde with β-nitrostyrene (Table 2, entry 1) resin **4** compares favorably with α,α-diphenylprolinol trimethylsilyl ether, which avoids the use of a large excess of acetaldehyde and employs a halved catalyst loading.[15] Thus, adduct **5a** can be prepared in 96% enantiomeric excess (*ee*), which deserves special comment given the reported interest in α-unsubstituted-γ-nitroaldehydes and general interest in the organocatalytic reactions of acetaldehyde.[15,16]

The catalytic activity of **4** showed a remarkable dependency on the structure of the aldehyde donor. Thus, fast reactions were observed for linear, short-chain aldehydes propionaldehyde and butanal (Table 2, entries 2 and 3), whereas the reaction time increased significantly with chain length (Table 2, entries 4 and 5). In all of these cases, the yields and enantioselectivities of the major *syn* products were excellent. Branching at the β position of the aldehyde had a detrimental effect on reaction rate (Table 2, entries 6 and 7) and α branching (Table 2, entry 8) completely blocked the

reaction. Ketones, such as acetone and cyclohexanone, were also tested as Michael donors but they were found to be completely unreactive.

With respect to the Michael acceptor, various substituted nitroolefins were tested. Under the optimized conditions, the addition of propionaldehyde to β-substituted aromatic nitroalkenes gave the expected *syn* adducts in excellent yields and enantioselectivities after short reaction times, independent of the electronic properties of the aryl or heteroaryl substituent (Table 2, entries 9–11). Reaction time increased notably when the aromatic substituent was not conjugated with the nitroolefin (Table 2, entry 12) and for aliphatic nitroolefins (Table 2, entries 13 and 14), although the Michael products **5l–n** were obtained in high yield and excellent enantioselectivity.



Scheme 5. Origin of the substrate selectivity [aldehydes (ald) versus ketones (ket)] in the Michael addition of carbonyl compounds to β-nitrostyrene catalyzed by **4**.

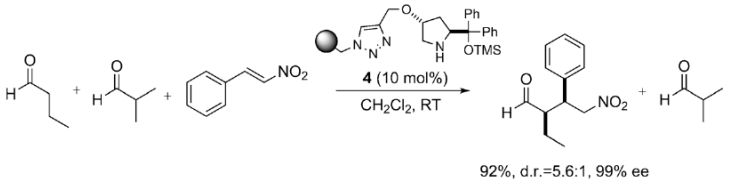
To ascertain if selectivity for linear aldehydes could be achieved in the presence of branched ones, we tested resin **4** in the Michael reaction of a mixture of butanal and 2-methylpropanal, with the composition that resulted from the Rh-catalyzed hydroformylation of propene and β-nitrostyrene in the presence of **4** (**4**/β-nitrostyrene/butanal/2-methylpropanal 0.1:1.0:2.4:1.5; see Scheme 4). Gratifyingly, under these conditions, only the linear aldehyde underwent Michael addition with no decrease in enantioselectivity (99% *ee*, compared to Table 2, entry 3).

However, the reaction time required for complete conversion (92% isolated yield) under these conditions was substantially extended (24 vs. 5 h), which suggested that unproductive enamines of 2-methylpropanal could be formed during the reaction and lead to a decrease in the concentration of the viable enamine intermediate. This suggestion is reinforced by the results of competition experiments that involved pentanal and cyclohexanone. When an equimolar mixture of these substrates was treated with β-nitrostyrene, the required time for the complete conversion of pentanal extended from 27 to 55 h. Even more noteworthy, when the cyclohexanone/pentanal ratio was changed to 13:1, the reaction time increased to 7 d. The retardation effect exerted by branched aldehydes or ketones can be rationalized through the equilibria represented in Scheme 5.

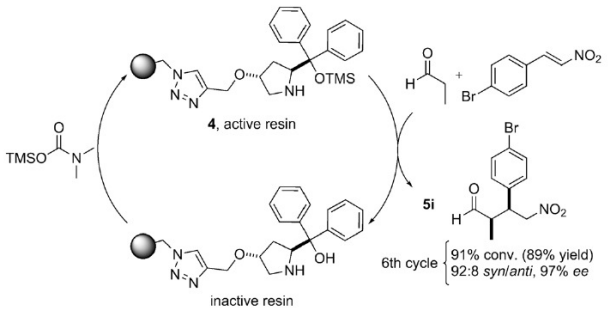
As already mentioned, the insoluble nature of the polymer allows for catalyst recovery by simple filtration. However, the recycling process can be limited by deactivation effects and, in the case of α,α-diphenylprolinol silyl ethers, the lability of the silyl ether group towards hydrolysis[12r] makes the reuse of the organocatalyst sometimes difficult. In our case, a complete absence of catalytic activity was observed in the Michael reaction of a resin that bore free hydroxyl groups on the α,α-diphenylprolinol moiety.

After extensive experimentation, we were able to address the deactivation problem of catalyst **4** by selective reprotection of the hydroxyl groups of inactive diphenylprolinol-type resins through brief treatment with trimethylsilyl *N,N*-dimethylcarbamate[17] in hexane/acetonitrile. This simple procedure leads to full recovery of the catalytic activity of the supported organocatalyst **4** and makes its reuse possible. Thus, in six consecutive cycles of reaction/reconditioning, the excellent performance of resin **4** in the Michael addition of propionaldehyde to 4-bromo-β-nitrostyrene remained intact (Scheme 6). Interestingly, the reactivation procedure does not represent any significant inconvenience from a practical point of view. Because the only byproduct formed in the process is dimethylamine, the reactivated resin can be directly reused after washing out any excess silylating reagent.

Synthesis and evaluation of polystyrene-supported (*S*)-α,α-diphenylprolinol methyl ether (11) in the Michael reaction of aldehydes and nitroalkenes: Although the origin of the deactivation of resin **4** was elucidated and properly solved, we were interested in the development of more robust polymer-supported diphenylprolinol-type catalysts with the ultimate goal of performing the present reaction in a continuous-flow manner. Therefore, we aimed

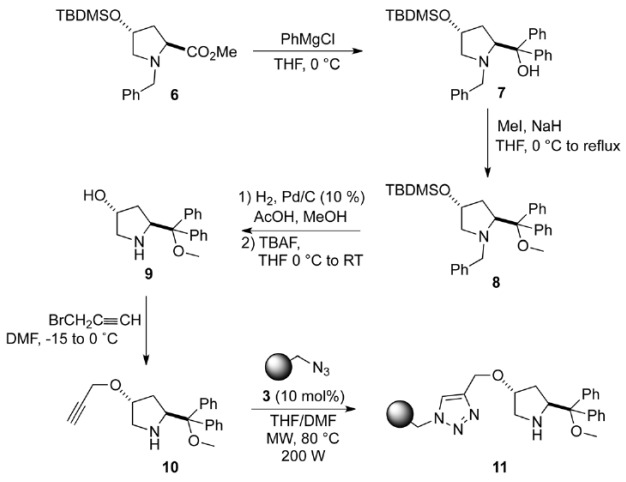


Scheme 4. Selective Michael addition of butanal to β-nitrostyrene in the presence of 2-methylpropanal catalyzed by **4**.



Scheme 6. Reconditioning and reuse of resin **4**.

to prepare and evaluate polymer-supported diphenylprolinol methyl ether (**11**), which should be stable under the standard reaction and recycling conditions, and not show hydrolytic deactivation. The synthesis of resin **11** is explained in detail in the Supporting Information and summarized in Scheme 7.

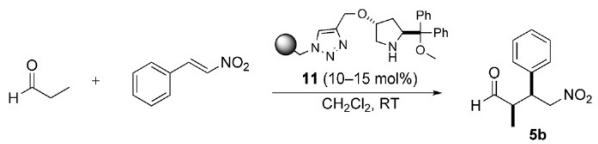


Scheme 7. Synthesis of the polymer-supported organocatalyst **11**.

To avoid the difficulties associated with the small-scale preparation of a non-supported counterpart,[18] our synthetic approach started with the preparation of compound **6** by selective protection of commercially available (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride. Grignard addition and subsequent methylation of the resulting tertiary alcohol provided the intermediate **8**, which was sequentially deprotected to give key intermediate 4-hydroxy diphenylprolinol methyl ether (**9**). Propargylation of **9** led to the required derivative **10**, suitable for a **TTM-Cu**-mediated click reaction with azidomethyl polystyrene.

Resin **11** was evaluated in the Michael addition of propionaldehyde to (*E*)-β-nitrostyrene (Table 3). Under the previously optimized conditions for catalyst **4** (Table 3, entry 1), the reaction proceeded slowly and with lower selectivity than with the silylated resin **4**. The addition of benzoic

Table 3. Evaluation of organocatalyst **11** in the Michael addition of propionaldehyde to (*E*)-β-nitrostyrene.[a]



	Additive (10 mol %)	*t* [h]	Yield[b] [%]	d.r.[c]	*ee*[d] [%]
1	none	96	51	80:20	85
2	PhCOOH	48	63	79:21	92
3[e]	PhCOOH[f]	48	53	82:18	90
4	4-NO_2PhCOOH	48	35	2:1	82
5[g]	PhCOOH	48	55	93:7	93
6[h]	PhCOOH	60	72	95:5	93

[a] General conditions: (*E*)-β-nitrostyrene (0.2 mmol), propionaldehyde (0.3 mmol), **11** (0.02 mmol), solvent (1 mL), RT. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by chiral HPLC analysis. [e] Catalyst **11** (0.03 mmol). [f] Benzoic acid (15 mol %). [g] (*E*)-β-nitrostyrene (1.5 equiv). [h] (*E*)-β-nitrostyrene (3 equiv).

acid as a co-catalyst (Table 3, entry 2) led to a slight improvement in the activity of catalyst **11**, although deactivation was observed (after approximately 48 h) before full conversion could be achieved.

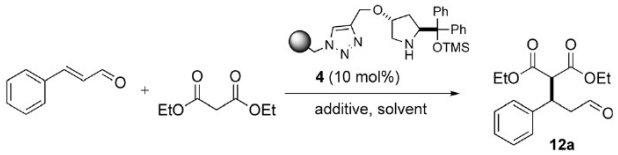
On the other hand, the addition of benzoic acid had a positive effect on the enantioselectivity of the process, which increased from 85 to 92 % *ee*, whereas the diastereoselectivity did not experience any change. The use of an additional 5 mol % of catalyst and co-catalyst did not change the results significantly (Table 3, entry 3). In turn, addition of the more acidic *p*-nitrobenzoic acid had a negative effect on both the conversion and stereoselectivity (Table 3, entry 4). In light of recently published kinetic studies, which revealed that the rate-limiting steps in the case of peptide-organocatalyzed conjugate addition reactions between aldehydes and nitroolefins are both the reaction of the enamine with the electrophile and the hydrolysis of the resulting imine,[19] we decided to perform the Michael addition of propanal to (*E*)-β-nitrostyrene with 1.0:1.5 and 1:3 molar ratios of aldehyde/nitroolefin (Table 3, entries 5 and 6, respectively). In these cases, the excess of nitrostyrene led to the Michael adduct **5b** with good enantioselectivity and highly improved diastereoselectivity relative to the previous results, even increasing the reaction time, although complete conversion was not achieved. Based on these initial experiments, we can envisage that although polystyrene-supported methyl ether **11** does not present the problem of ether cleavage under mild reaction conditions, it would show worse performance as a catalyst in the Michael addition of aldehydes to nitroolefins relative to **4**. This demonstrates, once again, the crucial role exerted by the *O*-silyl protecting group in the control of catalytic activity and selectivity of diarylprolinol ether derivatives.

Conjugate additions of malonates to α,β-unsaturated aldehydes catalyzed by 4: Secondary amines readily experience

condensation reactions with aldehydes or ketones to form intermediate iminium cations. These species are characterized by a low-lying LUMO and can often be trapped by nucleophiles before proton loss converts them into imines (primary amines) or enamines (secondary amines). This nucleophilic trapping is the fundamental event in iminium-type aminocatalysis. Focusing on conjugate addition reactions, a broad range of nucleophilic intermediates, such as nitroalkanes, nitroesters, malonates, and ketoesters, among others, have been used for conjugate addition to α,β-unsaturated systems assisted by iminium-type aminocatalysis.[20] The modularity of the products that arise from this process makes them valuable building blocks in organic chemistry. Chiral secondary amines, such as imidazolidinone derivatives[21] and *O*-TMS-protected diarylprolinols,[22] have shown high efficiency as catalysts by activating α,β-unsaturated systems through iminium-type mechanisms. Through the use of recoverable organocatalysts, positive economic and environmental aspects could complement this synthetic efficiency.

In view of our recent results obtained with dimethyl 3-oxoglutarate,[5g] we decided to test the **4** in the reaction of α,β-unsaturated aldehydes with dialkyl malonates.[23] The addition of diethyl malonate to cinnamaldehyde was selected as a model reaction and the results from the preliminary screening of the reaction conditions are shown in Table 4. Initially, we chose dichloromethane as the solvent because of its good swelling properties for resin **4** and the optimal performance of this solvent in the Michael addition of aldehydes to nitroalkenes discussed above. When the reaction was performed in the absence of additives, poor activity was recorded, with only 24% of conversion after 96 h (Table 4, entry 1), although enantioselectivity was high (90% *ee*). Benzoic acid (30 mol%), a commonly employed acidic cocatalyst for iminium-catalyzed processes, was tested as an additive to promote conversion, but no improvement was observed (Table 4, entry 2). As an alternative, we attempted to increase the activity of catalyst **4** by Lewis base/Brønsted base co-operative catalysis.[23c] Thus, when lithium acetate was used as a Brønsted base to activate the malonate reagent complete conversion was recorded after 36 h and enantioselectivity was preserved (Table 4, entry 3). To investigate the effect of the aldehyde/malonate ratio in the reaction, we tried the same reaction with diethyl malonate (1.0 equiv), cinnamaldehyde (1.5 equiv) and lithium acetate (10 mol%). No change in enantioselectivity was observed, but conversion suffered a dramatic decrease and only 25% of the starting material had reacted after 24 h (Table 4, entry 4). Tetrahydrofuran was tested as a solvent for the optimal swelling of **4** but, surprisingly, resulted in total loss of catalytic activity (Table 4, entry 5). Water was also tested as a solvent, but after 96 h conversion was only 49% and the *ee* had decreased to 53% (Table 4, entry 6). Thus, the possible environmental advantages presented by this solvent are outbalanced by its probable negative effect on iminium ion formation and malonate reactivity. Finally, to mitigate the requirement for long reaction times, we decided to perform the reaction under low-power microwave (MW) irradiation, in line with our previous experience in other reactions catalyzed by polystyrene-supported species.[5e,24] Gratifyingly, a notable acceleration of the reaction was observed (Table 4, entry 7).

Table 4. Optimization of the reaction conditions for the asymmetric addition of diethyl malonate to cinnamaldehyde catalyzed by **4**.[a]



	Solvent	Additive (30 mol%)	*t* [h]	Conv[b] [%]	*ee*[c] [%]
1	CH_2Cl_2	none	96	24	90
2	CH_2Cl_2	PhCOOH	24	8	n.d.
3	CH_2Cl_2	LiOAc	36	>99	90
4[d]	CH_2Cl_2	LiOAc[e]	24	25	90
5	THF	LiOAc	48	0	n.d.
6	H_2O	LiOAc	96	49	53
7[f]	CH_2Cl_2	LiOAc	6	93	90

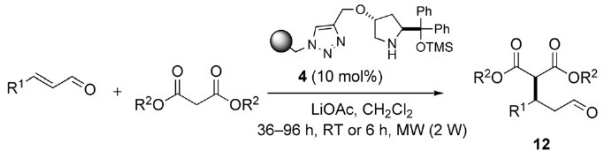
[a] General conditions: cinnamaldehyde (0.2 mmol), diethyl malonate (0.6 mmol), **4** (0.02 mmol), solvent (1 mL), RT. [b] Conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Reaction carried out with a 1:1.5 molar ratio of aldehyde/malonate. [e] LiOAc (10 mol%). [f] Reaction carried out under MW irradiation (2 W) in CH_2Cl_2 (0.3 mL).

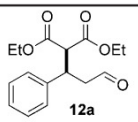
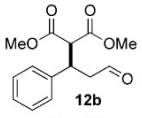
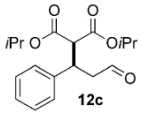
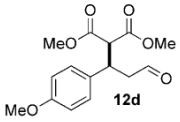
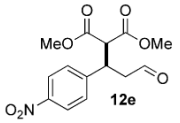
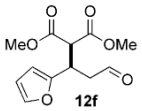
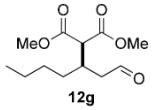
Under low-power MW irradiation (2 W), the reaction temperature increased from 23 to 30°C and the reaction time was reduced by a factor of six (Table 4, entry 7 versus 3), although no change in enantioselectivity was noticed. Under these optimized conditions, the scope of the reaction was studied. A series of dialkyl malonates and α,β-unsaturated aldehydes were tested and the results are presented in Table 5.

The addition of dimethyl, diethyl, or diisopropyl malonates to cinnamaldehyde was studied at room temperature and under MW irradiation (2 W, 6 h). In all cases, the expected products **12a–c** were obtained with full conversion and very high enantioselectivities (Table 5, entries 1–3). Branching in the alkyl moiety of the malonate ester (Table 5, entry 3) resulted in an extended reaction time for complete conversion to be achieved. Given the excellent enantioselectivity recorded from reaction with dimethyl malonate (Table 5, entry 2), we evaluated the addition of this nucleophile to a small family of α,β-unsaturated aldehydes. Good yields and high enantioselectivities were obtained from the reactions of cinnamaldehyde derivatives with either an electron-donating or electron-withdrawing group on the *para* position of the ring (Table 5, entries 4 and 5).

Full conversion was again observed in the addition of dimethyl malonate to heterocyclic α,β-unsaturated aldehyde 3-(2-furyl)acrolein, but the enantioselectivity was substantially lower than for previous examples (Table 5, entry 6). To exemplify enals lacking extended conjugation, 2-heptenal was also tested as an electrophile in the reaction (Table 5, entry 7) and afforded the addition product **12g** with good yield and enantioselectivity. As a general observation, the

Table 5. Substrate scope in the asymmetric addition of dialkyl malonates to α,β-unsaturated aldehydes organocatalyzed by **4**.[a]



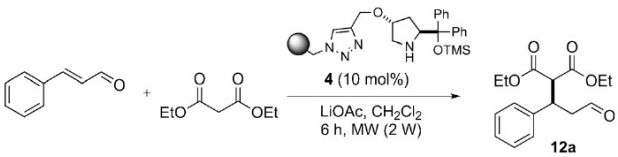
	Product	*t* [h]	Yield[b,c] [%]		*ee*[b,d] [%]	
1	 **12a**	36	81	(88)	91	(90)
2	 **12b**	36	86	(80)	99	(99)
3	 **12c**	72	85	(63)	90	(90)
4	 **12d**	96	87	(85)	94	(92)
5	 **12e**	36	90	(89)	92	(90)
6	 **12f**	96	75	(82)	77	(78)
7	 **12g**	96	85	(76)	79	(83)

[a] General conditions: α,β-unsaturated aldehyde (0.2 mmol), dialkyl malonate (0.6 mmol), LiOAc (0.06 mmol), **4** (0.02 mmol), CH_2Cl_2 (0.3 mL), RT or MW irradiation (6 h, 2 W). [b] The results of the experiments performed under MW irradiation are shown in parentheses. [c] Isolated yield. [d] Determined by chiral HPLC analysis.

results obtained from this screening showed that the co-operative catalytic system **4**/LiOAc is highly efficient for the addition of malonates to α,β-unsaturated aldehydes with the advantage of easy separation of the polymer-supported catalyst from the obtained products. Experimentally, activation of the reactions with low-power microwave irradiation (2 W) is clearly advantageous over execution of the reactions at room temperature.

The possibility of recycling and reusing resin **4** was next studied. As shown in Table 6, conversion decreased considerably when the catalytic system **4**/LiOAc was directly reused after separation of the reaction mixture and a dichloromethane wash (Table 6, cycle 2). Addition of fresh LiOAc in the next cycle did not improve the catalytic activity (Table 6, cycle 3); nevertheless, enantioselectivity remained unchanged over the three runs. As already mentioned, we could reactivate resin **4** in the Michael addition of aldehydes to nitroolefins by reprotection of the inactive polymer-supported diphenylprolinol with trimethylsilyl *N,N*-dimethylcarbamate.[17] In this particular case, such treatment had a positive effect but did not lead to complete recovery of the catalytic activity of **4** (Table 6, cycle 4).

Table 6. Recycling experiments of catalyst **4** in the asymmetric addition of diethyl malonate to cinnamaldehyde.[a]



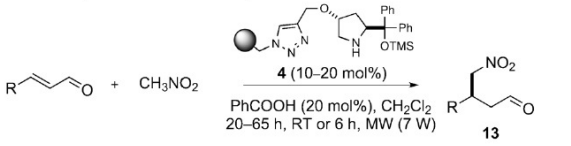
Cycle	*t* [h]	Conv[b] [%]	*ee*[c] [%]
1	6	93	90
2	6	73	90
3[d]	6	53	90
4[e]	6	77	90

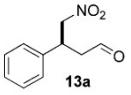
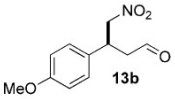
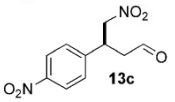
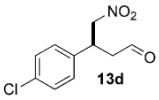
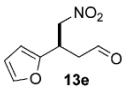
[a] General conditions: cinnamaldehyde (0.2 mmol), diethyl malonate (0.6 mmol), LiOAc (0.06 mmol), **4** (0.02 mmol), CH_2Cl_2 (0.3 mL), MW irradiation (2 W). [b] Conversion was determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [c] Determined by chiral HPLC analysis. [d] Additional LiOAc (0.06 mmol) was added. [e] Resin reconditioned by treatment with trimethylsilyl *N,N*-dimethylcarbamate (see reference [5f].

To test the performance of polystyrene-supported methyl ether **11** in reactions taking place via iminium ion intermediates, **11** (10 mol%) was also tested as catalyst in the addition of diethyl malonate to cinnamaldehyde in the presence of LiOAc (30 mol%) in CH_2Cl_2 under MW irradiation (2 W) to accelerate the reaction. After 6 h, **12a** could be isolated in 27% yield and 86% *ee*. This result confirmed our initial impression (see above) on the lower catalytic efficiency of **11** relative to **4**.

Addition of nitromethane to α,β-unsaturated aldehydes catalyzed by 4: Further proof of the effectiveness of resin **4** in reactions that take place through iminium ion activation could be obtained from its notable performance in the iminium-catalyzed enantioselective synthesis of γ-nitro aldehydes by a Henry-type reaction of nitromethane with α,β-unsaturated aldehydes.[5h,25] Preliminary experiments in the addition of nitromethane to cinnamaldehyde under the optimal reaction conditions reported for α,α-diphenylprolinol-type catalysts[5h,25] [MeOH, catalyst (10 mol%), benzoic acid co-catalyst (10–20 mol%)] resulted in poor conversions. Much better results were obtained in dichloromethane, an optimal swelling media for **4**, which was adopted as the solvent for this study (Table 7). On the other hand, the use of LiOAc (20 mol%) as a co-catalyst in the addition of nitromethane to cinnamaldehyde resulted in a significant reduction of activity, therefore its use was no longer considered. Thus, the selected reaction conditions were a combination of **4** and benzoic acid in dichloromethane.

Table 7. Evaluation of organocatalyst **4** in the Michael addition of nitromethane to α,β-unsaturated aldehydes.[a]



	Product	T [°C]	t [h]	Conv[b] [%]	Yield[c] [%]	ee[d] [%]
1[e]	 **13a**	RT	65	75	52	96
2		RT	56	>99	86	96
3		45	20	83	75	95
4[e]		45	30	64	51	93
5[f]		45	6	>99	61	96
6[f]	 **13b**	45	6	>99	80	91
7[f]	 **13c**	45	6	>99	88	90
8[f]	 **13d**	45	6	>99	85	90
9[f]	 **13e**	45	6	>99	31	94
10[g]		30	7	85	52	95

[a] General conditions: α,β-unsaturated aldehyde (0.2 mmol), nitromethane (0.6 mmol), benzoic acid (0.04 mmol), **4** (0.04 mmol), CH_2Cl_2 (0.5 mL). [b] Conversion determined by ^1H NMR spectroscopy of the crude reaction mixture. [c] Isolated yield. [d] Determined by chiral GC or HPLC analysis. [e] Catalyst **4** (10 mol%). [f] Reaction performed under MW irradiation (7 W). [g] Reaction performed under MW irradiation (3 W).

When **4** (10 mol%) and benzoic acid (20 mol%) were used to promote the reaction at room temperature, only moderate conversion to **13a** was recorded after 65 h (Table 7, entry 1). However, the enantioselectivity compared very favorably with that recorded when soluble α,α-diphenylprolinol trimethylsilyl ethers were used.[5h,25] Increasing the catalyst loading (20 mol%) was enough to ensure complete conversion, high yield, and excellent enantiomeric excess after a reasonable reaction time (Table 7, entry 2). Importantly, we also found that heating the reaction mixture at 45°C accelerated the reaction but compromised both the yield and enantioselectivity (Table 7, entries 3 and 4). Interestingly, when the reaction was performed at this temperature under MW irradiation (7 W), we were able to significantly reduce the reaction time and achieve total conversion of cinnamaldehyde without any detriment to the enantioselectivity (Table 7, entry 5). The observed decrease in the isolated yield under these conditions can be attributed to poor stability of the aldehyde product.[25b]

The beneficial effect of MW activation in this reaction was additionally confirmed when a representative set of α,β-unsaturated aldehydes was evaluated under the same reaction conditions. High yields and selectivities were recorded with both electron-poor and electron-rich substituted cinnamaldehydes (Table 7, entries 6–8). With 3-(2-furyl)acrolein (Table 7, entries 9 and 10) the reaction proceeded more satisfactorily when run under MW irradiation at 30°C, and gave γ-nitro aldehyde **13e** in moderate yield but with excellent enantioselectivity.

Conclusion

An insoluble polystyrene-supported diarylprolinol silyl ether (**4**) was prepared and used as a highly efficient, reusable organocatalyst for Michael additions that proceed by enamine or iminium ion catalysis. In reactions via enamine intermediates, **4** exhibits a remarkable preference for linear aldehyde donors; this preference can be used in practice for the differentiation between linear and branched aldehydes in their reactions with nitroolefins. In reactions taking place via iminium ion intermediates, **4** efficiently mediates the addition of dialkyl malonates and nitromethane to α,β-unsaturated aldehydes. As a general observation, **4** exhibits a catalytic performance comparable, or superior, to monomeric, soluble diarylprolinol silyl ethers and offers the additional advantages of simplified reaction workup, easy catalyst recovery, and the possibility of catalyst reuse. In an attempt to extend the life cycle of **4** for repeated use, a polystyrene-supported diarylprolinol methyl ether (**11**) was also prepared and evaluated. However, the catalytic characteristics of this species are inferior to those of **4**.

Experimental Section

General procedure for the Michael addition of aldehydes to nitroolefins catalyzed by 4 or 11 (GP1): Nitroolefin (0.2 mmol) and catalyst **4** (46.1 mg, 10 mol% according to the functionalization (f) = 0.462 mmol g^{-1}) or **11** (45.1 mg, 10 mol%, f = 0.443 mmol g^{-1}) were mixed with the aldehyde (0.3 mmol) in CH_2Cl_2 (1.0 mL). The suspension was stirred at RT for the time specified in Table 2 and filtered to separate the solid catalyst. The resin was washed with CH_2Cl_2 and the combined organic extracts were concentrated under reduced pressure. A ^1H NMR spectrum was recorded to calculate the conversion and d.r. For volatile starting aldehydes, the Michael adduct was obtained as the evaporation residue without further purification. In other cases, purification by flash chromatography on silica gel (EtOAc/hexane) afforded the Michael adduct. The enantiomeric excess was determined by HPLC on a chiral stationary phase (Chiralpak IB or Chiralcel AD-H columns).

All of the prepared products are known and spectroscopic data are, in all cases, in agreement with the published data. Compounds **5a–k** have been described in a preliminary communication of this work.[5f]

Starting nitroolefins (*E*)-(4-nitrobut-3-en-1-yl)benzene, (*E*)-(2-nitrovinyl)cyclohexane, and (*E*)-3-methyl-1-nitrobut-1-ene were prepared by literature procedures.[26]

(2*R*, 3*R*) 2-Methyl-3-nitromethyl-5-phenyl-pentanal (5l):[27] Compound **5l** was prepared from *E*-(4-nitrobut-3-en-1-yl)benzene and propionaldehyde according to **GP1** in 94% yield (44.2 mg, 0.188 mmol) as an inseparable mixture of two diastereomers. 95% *ee* by HPLC: IB (hexane/*i*PrOH 95:5, 1.0 mL min^{-1}, λ = 220 nm); retention time (t_R) (major) = 18.6 min, t_R(minor) = 21.3 min.

(2*R*, 3*R*)-3-Cyclohexyl-2-methyl-4-nitrobutyraldehyde (5m):[12c] Compound **5m** was prepared from *E*-(2-nitrovinyl)cyclohexane and propionaldehyde according to **GP1** in 89% yield (38 mg, 0.178 mmol) as an inseparable mixture of two diastereomers. 97% *ee* by HPLC: AD-H (hexane/*i*PrOH 99:1, 1.0 mL min^{-1}, λ = 213 nm); t_R(major) = 13.3 min, t_R(minor) = 16.7 min.

(2*R*, 3*R*)-2,4-Dimethyl-3-nitromethylpentanal (5n):[28] Compound **5n** was prepared from *E*-3-methyl-1-nitrobut-1-ene and propionaldehyde according to **GP1** in 84% yield (29 mg, 0.168 mmol) as an inseparable mixture of two diastereomers. 99% *ee* by HPLC: AD-H (hexane/*i*PrOH 99:1, 0.8 mL min^{-1}, λ = 210 nm); t_R(major) = 12.6 min, t_R(minor) = 13.9 min.

General procedure for the addition of malonates to α,β-unsaturated aldehydes (GP2): Resin **4** (10 mol%, f = 0.462 mmol g^{-1}) and lithium acetate (30 mol%) were placed in a vial. CH_2Cl_2 (1 mL) was added, followed by the α,β-unsaturated aldehyde (0.2 mmol) and dialkyl malonate (0.6 mmol). The mixture was stirred at RT for the time indicated in Table 4, until total conversion was confirmed by ^{1}H NMR spectroscopy. The resin was filtered off and rinsed with CH_2Cl_2 (3 mL). The combined organic extracts were concentrated under reduced pressure and the crude product purified by flash chromatography on silica gel (hexane/diethyl ether, 10:1).

General procedure for the addition of malonates to α,β-unsaturated aldehydes under MW irradiation (GP3): Resin **4** (10 mol%, f = 0.462 mmol g^{-1}), lithium acetate (30 mol%), and CH_2Cl_2 (0.3 mL) were added to a MW vial. α,β-Unsaturated aldehyde (0.2 mmol) and dialkyl malonate (0.6 mmol) were added. The mixture was irradiated at 2 W power (30°C) for 6 h. The resin was filtered off and rinsed with CH_2Cl_2 (3 mL). The combined organic extracts were concentrated under reduced pressure and the crude product purified by flash chromatography (hexane/diethyl ether, 10:1). Products **12a–g** are known compounds, and the spectroscopic data are in agreement with the published data.[23c–g,29]

(*R*)-Diethyl 2-(3-oxo-1-phenylpropyl)malonate (12a):[23c] Compound **12a** was obtained from (*E*)-cinnamaldehyde and diethyl malonate with catalyst **4** after 36 h in 81% yield (47.4 mg, 0.162 mmol) following **GP2**. When **GP3** was followed, **12a** was obtained in 88% yield (51.5 mg, 0.176 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mL min^{-1}, λ = 210 nm); t_R(major) = 17.5 min, t_R(minor) = 21.9 min.

(*R*)-Dimethyl 2-(3-oxo-1-phenylpropyl)malonate (12b):[23c] Compound **12b** was obtained from (*E*)-cinnamaldehyde and dimethyl malonate with catalyst **4** after 36 h in 86% yield (45.5 mg, 0.172 mmol) following **GP2**. When **GP3** was followed, **12b** was obtained in 80% yield (42.3 mg, 0.16 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mL min^{-1}, λ = 210 nm); t_R(major) = 20.4 min, t_R(minor) = 23.8 min.

(*R*)-Diisopropyl 2-(3-oxo-1-phenylpropyl)malonate (12c):[23c] Compound **12c** was obtained from (*E*)-cinnamaldehyde and diisopropyl malonate with catalyst **4** after 72 h in 85% yield (54.5 mg, 0.17 mmol) following **GP2**. When **GP3** was followed, **12c** was obtained in 63% yield (40.3 mg, 0.126 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.5 mL min^{-1}, λ = 210 nm); t_R(major) = 14.4 min, t_R(minor) = 17.6 min.

(*R*)-2-Isopropyl 3-methyl 2-((*R*)-1-(4-methoxyphenyl)-3-oxopropyl)malonate (12d):[23g] Compound **12d** was obtained from (*E*)-3-(4-methoxyphenyl) acrylaldehyde and dimethyl malonate with catalyst **4** after 96 h in 87% yield (56 mg, 0.174 mmol) following **GP2**. When **GP3** was followed, **12d** was obtained in 85% yield (54.8 mg, 0.17 mmol). HPLC: AD-H (hexane/*i*PrOH 90:10, 0.8 mL min^{-1}, λ = 210 nm); t_R(major) = 25.3 min, t_R(minor) = 27.1 min.

(*R*)-1-Isopropyl 3-methyl 2-((*R*)-1-(4-nitrophenyl)-3-oxopropyl)malonate (12e):[23g] Compound **12e** was obtained from (*E*)-3-(4-nitrophenyl)acrylaldehyde and dimethyl malonate with catalyst **4** after 36 h in 90% yield (61 mg, 0.18 mmol) following **GP2**. When **GP3** was followed, **12e** was obtained in 89% yield (60 mg, 0.178 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.8 mL min^{-1}, λ = 210 nm); t_R(major) = 23.8 min, t_R(minor) = 25.4 min.

(*R*)-1-Isopropyl 3-methyl 2-((*R*)-1-(furan-2-yl)-3-oxopropyl)malonate (12f):[23g] Compound **12f** was obtained from (*E*)-3-(2-furyl)acrylaldehyde and dimethyl malonate with catalyst **4** after 96 h in 75% yield (42.7 mg, 0.15 mmol) following **GP2**. When **GP3** was followed, **12f** was obtained in 82% yield (46.3 mg, 0.164 mmol). HPLC: AD-H (hexane/*i*PrOH 80:20, 0.8 mL min^{-1}, λ = 210 nm); t_R(minor) = 20.3 min, t_R(major) = 22.2 min.

(*R*)-1-Isopropyl 3-methyl 2-((*R*)-1-oxoheptan-3-yl)malonate (12g):[29] Compound was obtained from (*E*)-hept-2-enal and dimethyl malonate with catalyst **4** after 96 h in 85% yield (46.3 mg, 0.17 mmol) following **GP2**. When **GP3** was followed **12g** was obtained in 76% yield (41.4 mg, 0.152 mmol). HPLC: IC (heptane/*i*PrOH 90:10, 1 mL min^{-1}, mass-APCI(−)); t_R(major) = 13.3 min, t_R(minor) = 14.1 min.

General procedure for the Michael addition of nitromethane to cinnamaldehyde (GP4): Catalyst **4** (10–20 mol%, f = 0.462 mmol g^{-1}) and benzoic acid (4.87 mg, 0.04 mmol) were placed in a vial. CH_2Cl_2 (0.5 mL), cinnamaldehyde (0.2 mmol, 25 mL), and nitromethane (0.6 mmol, 32 mL) were added successively. The mixture was stirred at the indicated temperature for the time noted in Table 7. The resin was filtered and rinsed with CH_2Cl_2. The combined organic extracts were concentrated under reduced pressure and the crude product purified by flash chromatography (silica gel, hexane/EtOAc 10:1).

General procedure for the Michael addition of nitromethane to α,β-unsaturated aldehydes under MW irradiation (GP5): Catalyst **4** (86.6 mg, 0.04 mmol, f = 0.462 mmol g^{-1}) and benzoic acid (4.87 mg, 0.04 mmol) were placed in a MW vial. CH_2Cl_2 (0.5 mL), α,β-unsaturated aldehyde (0.2 mmol), and nitromethane (0.6 mmol, 32 mL) were added successively. The mixture was irradiated at 7 W (45°C) for 6 h in a MW reactor. The resin was filtered and rinsed with CH_2Cl_2. Evaporation of the solvent under reduced pressure afforded the desired product, which was purified by flash chromatography (silica gel, hexane/EtOAc 10:1). Products **13a–e** are known compounds and the spectroscopic data are in agreement with the published data.[5h,25a]

(*S*)-4-Nitro-3-phenylbutanal (13a):[25a] Compound **13a** was obtained from cinnamaldehyde in 86% yield following **GP4**, and in 61% yield following **GP5**. GC-MS: Chiraldex G-TA (130°C isotherm, 1.5 mL min^{-1}); t_R(minor) = 133.4 min, t_R(major) = 139.4 min.

(*S*)-3-(4-Methoxyphenyl)-4-nitrobutanal (13b):[25a] Compound **13b** was obtained from 3-(4-methoxyphenyl)propenal in 80% yield following **GP5**. HPLC: IB (hexane/*i*PrOH 85:15, 1.0 mL min^{-1}, λ = 254 nm); t_R(minor) = 11.9 min, t_R(major) = 12.5 min.

(*S*)-4-Nitro-3-(4-nitrophenyl)butanal (13c):[5h] Compound **13c** was obtained from 3-(4-nitrophenyl)propenal in 88% yield following **GP5**. HPLC: IC (hexane/*i*PrOH 90:10, 1.0 mL min^{-1}, λ = 254 nm); t_R(minor) = 41.3 min, t_R(major) = 44.4 min.

(*S*)-3-(4-Chlorophenyl)-4-nitrobutanal (13d):[25a] Compound **13d** was obtained from 3-(4-chlorophenyl)propenal in 85% yield following **GP5**. HPLC: IC (hexane/*i*PrOH 10:1, 1.0 mL min^{-1}, λ = 240 nm); t_R(minor) = 18.9 min, t_R(major) = 20.8 min.

(*S*)-3-(2-Furyl)-4-nitrobutanal (13e):[25a] Compound **13e** was obtained from 3-furyl-propenal in 52% yield following a modified version of **GP5** with irradiation at 3 W for 7 h. GC-MS: Chiraldex G-TA (130°C isotherm, 1.5 mL min^{-1}); t_R(minor) = 49.9 min, t_R(major) = 54.0 min.

For general methods and for the synthesis and characterization of **11**, see the Supporting Information.

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Polystyrene-Supported Diarylprolinol Ethers as Highly Efficient Organocatalysts for Michael-Type reactions

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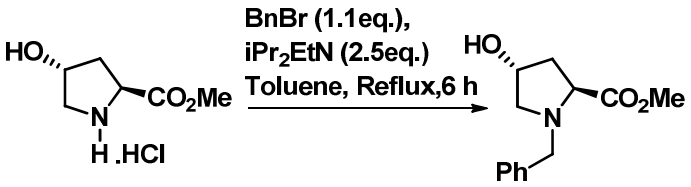
1. General remarks:

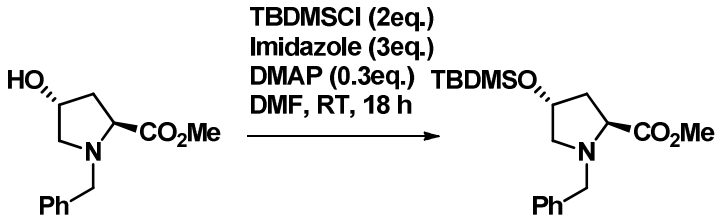
Unless otherwise stated, all commercial reagents were used as received and all reactions were carried out directly under open air. Merrifield resin (1% DVB, f = 0.53 mmol of Cl g^{-1} resin) was purchased from Novabiochem. In each case the extent of the supporting process and the functionalization of the final resin were determined by elemental analysis (%Cl for the starting Merrifield resin and %N for the functional resins **2**, **4** and **11**). The incorporation of the monomers onto the resins was in all cases >95%.[1] All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. NMR spectra were registered in a Bruker Advance 400 Ultrashield spectrometer in $CDCl_3$ at room temperature, operating at 400.13 MHz (^1H) and 100.63 MHz ($^{13}C\{^1H\}$). TMS was used as internal standard for ^1H-NMR and $CDCl_3$ for ^{13}C-NMR. Chemical shifts are reported in ppm referred to TMS. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier Instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Optical rotations were measured on a Jasco P-1030 polarimeter. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatograph (Serie1200), using Chiralcel AD-H, Chiralpak IA, IB and IC columns and guard columns. GC-MS was performed on Agilent Technologies chromatograph (Model 6890N), equipped with a mass Selective Detector 5973 Inert using Chiraldex G-TA (30 m x 0.25 mm, 0.12 mm) column. Racemic standard products were prepared using the same general procedures but using 10 mol% of (R,S)-α,α-diphenyl-2-pyrrolidinemethanol tert-butyldimethylsilyl ether as catalyst according to reported procedures in order to establish HPLC or GC conditions.

2. Synthesis of polystyrene-supported (*S*)-α,α-diphenylprolinol methyl ether (11):



(2*S*,4*R*)-methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate[2]

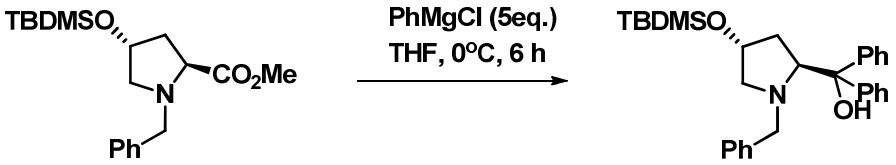
To a solution of *N*-Boc-*trans*-4-hydroxy-L-proline methyl ester hydrochloride (1.7 g, 9.4 mmol) in toluene (20.0 mL) were added *i*-PrNEt (4.1 mL, 23.6 mmol) and benzyl bromide (1.2 mL, 10.4 mmol) and the mixture was heated at reflux (110 ºC) for 6 h. Within this time the reaction mixture was turned into dark orange biphasic clear solution. After 6 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL). The organic materials were extracted with EtOAc (3 x 30 mL) and dried over Na_2SO_4. The product was obtained in 99% yield after solvent removal and used in the next step without any further purification. R_f = 0.17 (EtOAc/hexanes 9:1); $[\alpha]_D^{26}$ = –55.6 (*c* =1.29 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 - 7.26 (m, 5H), 4.47 - 4.44 (m, 1H), 3.90 (d, *J* = 12.92 Hz, 1H), 3.68 - 3.59 (m, 2H), 3.65 (s, 3H), 3.32 (dd, *J* = 10.16, 5.60 Hz, 1H), 2.47 (dd, *J* = 10.18, 3.78 Hz, 1H), 2.29 - 2.22 (m, 1H), 2.11 - 2.04 (m,1H), 1.80 - 1.76 (br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.0, 138.1, 129.1, 128.3, 127.2, 70.3, 63.6, 61.1, 58.1, 51.7, 39.6; IR (ATR): v= 3401, 3054, 2952, 2811, 1734, 1453, 1437, 1265 cm^{-1}.



(2*S*,4*R*)-methyl 1-benzyl-4-((*tert*-butyldimethylsilyl)oxy) pyrrolidine-2-carboxylate (6) [3]

To a stirred solution of (2*S*,4*R*)-methyl 1-benzyl-4-hydroxypyrrolidine-2-carboxylate (2.2 g, 9.3 mmol) in DMF (105 mL), imidazole (1.9 g, 27.9 mmol), *tert*-butyldimethylsilyl chloride (2.8 g, 18.6 mmol) and 4-dimethylaminopyridine (0.34 g,

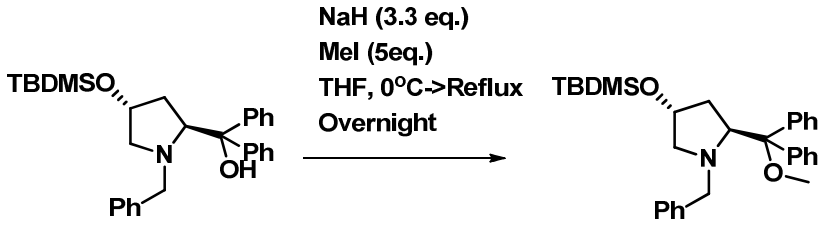
2.8 mmol) were added in this order. The reaction mixture was stirred at room temperature for 18 h. After quenching with MeOH (20 mL), the reaction mixture was diluted with EtOAc (50 mL) and washed with water (3 x 30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed chromatography using EtOAc:hexanes (1:19) as eluent. The product was obtained as colourless oil in 88 % yield. R_f= 0.26 (EtOAc/Hexanes 1:8); $[\alpha]_D^{26}$ = –30.6 (*c* = 1.25 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 - 7.24 (m, 5H), 4.42 - 4.39 (m, 1H), 3.91 (d, *J* = 12.80 Hz, 1H), 3.64 (s, 3H), 3.59 (d, *J* =12.80 Hz, 1H), 3.53 (t, *J*= 8.16 Hz, 1H), 3.26 (dd, *J* = 9.72, 5.76 Hz, 1H), 2.37 (dd, *J* = 9.72, 5.16 Hz, 1H), 2.22 - 2.15 (m, 1H), 2.05 - 1.99 (m, 1H), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 174.3, 138.1, 129.2, 128.2, 127.1, 70.5, 64.4, 61.7, 59.4, 51.8, 39.6, 25.8, 18.0, -4.8; IR (ATR): ν = 2951, 2929, 2856, 2802, 1748, 1735, 1494, 1470, 1454, 1251, 1094 cm^{-1}.



((2*S*,4*R*)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-2-yl)diphenyl-methanol (7)

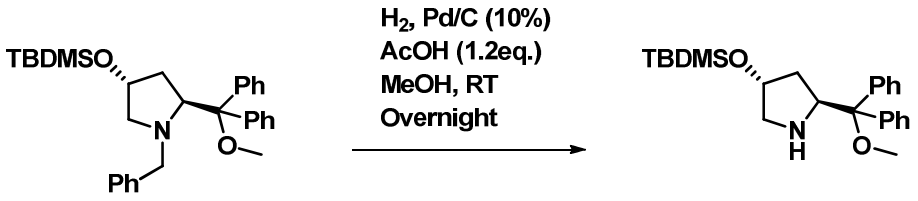
(2*S*,4*R*)-Methyl 1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidine-2-carboxylate (6) (2.8 g, 8.0 mmol) was dissolved in dry THF (60 mL) under N_2 and cooled at 0 ºC. PhMgCl (20.0 mL, 2 M solution in THF) was added dropwise within 20 min. The reaction mixture was stirred for 6 h, and then quenched with saturated aqueous NH_4Cl. THF was removed under reduced pressure to give a milky residue which was partitioned between CH_2Cl_2 and 1 N HCl solution. The organic layers were collected, washed with brine, dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by flash column chromatography (EtOAc/Hexanes 1:19) to give the product as slight yellow solid in 92 % yield. R_f= 0.38 (EtOAc/Hexanes 1:6); $[\alpha]_D^{27}$ = + 29.4 (c = 1.49 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.36 Hz, 2H), 7.59 (d, *J* = 7.16 Hz, 2H), 7.32 - 7.09 (m, 9H), 7.04 (d, *J* = 7.16 Hz, 2H), 4.97 (s, 1H), 4.36 (t, *J* = 7.84 Hz, 1H), 4.20 - 4.16 (m, 1H), 3.32 (d, *J* = 16.96 Hz, 2H), 2.96 (dd, *J* = 10.90, 4.38 Hz, 1H), 2.50 (dd, *J* =

10.90, 4.02 Hz, 1H), 1.85 - 1.83 (m, 1H), 0.89 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.9, 146.1, 139.9, 128.5, 128.2, 128.1, 128.0, 126.8, 126.5, 126.3, 125.7, 125.5, 71.5, 70.9, 62.2, 61.5, 39.0, 25.8, 17.9, –4.7, –4.8; IR (ATR): ν = 3346, 2952, 2928, 2855, 2802, 1494, 1471, 1252, 1028 cm^{-1}. HRMS (ESI+): m/z = 474.2817, calcd. for $C_{30}H_{40}NO_2Si$ [M+H]+: 474.2828



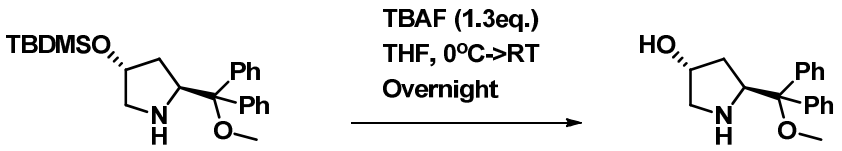
(2S,4*R*)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-2 (methoxydiphenylmethyl)-pyrrolidine (8)

((2*S*,4*R*)-1-Benzyl-4-((*tert*-butyldimethylsilyl)oxy)pyrrolidin-2-yl) diphenylmethanol (7) (1.7 g, 3.5 mmol) was dissolved in dry THF (25 mL) and transferred via cannula over NaH (95%, 0.294 g, 11.6 mmol), which was cooled in an ice bath. After stirring this mixture half an hour in an ice bath, MeI (1.1 mL, 17.6 mmol) was added. Then reaction mixture was allowed to warm to room temperature and hydrogen gas evolution was completed. Then, reflux started and reaction continued overnight. The reaction was quenched with aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer extracted twice with CH_2Cl_2. Combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Product was obtained as colorless oil in 98 % yield without further purification. R_f= 0.32 (EtOAc/ Hexanes 1:10); $[\alpha]_D^{27}$ = –73.7 (c = 1.41 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65-7.61 (m, 4H), 7.38 - 7.23 (m, 9H), 7.07 (d, *J* = 7.32 Hz, 2H), 4.14 - 4.05 (m, 2H), 3.54 (d, *J* = 12.69 Hz, 1H), 2.95 - 2.88 (m,1H), 2.92 (s, 3H), 2.43 (dd, *J* = 5.44, 9.44 Hz, 1H), 2.12 (dd, *J* = 6.82, 9.38 Hz, 1H), 1.93 - 1.89 (m, 2H), 0.75 (s, 9H), -0.18 (s, 3H), -0.2 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 140.8, 140.3, 138.8, 130.3, 130.2, 128.6, 128.0, 127.3, 127.2, 127.1, 126.4, 87.3, 70.6, 62.4, 61.0, 52.0, 37.9, 25.8, 17.9, - 4.9, -5.1; IR (ATR): ν = 3059, 3026, 2950, 2928, 2825, 1600, 1493, 1470, 1462, 1448, 1251, 1072 cm^{-1}; HRMS (ESI+) m/z = 488.2970, calcd. for $C_{31}H_{41}NO_2Si$ $[M+H]^+$: 488.2985.



(2*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2-(methoxydiphenylmethyl)-pyrrolidine (8b)

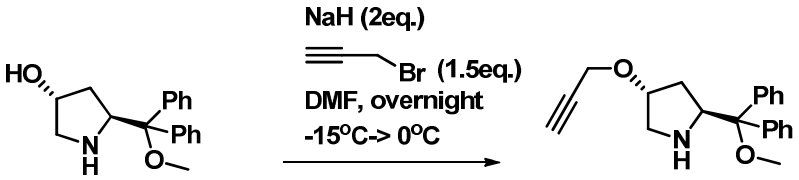
To (2*S*,4*R*)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-2- (methoxydiphenylmethyl)-pyrrolidine (8) (1.27 g, 2.6 mmol) in a flame-dried flask was added Pd on activated charcoal (10 %). The mixture was submitted to hydrogenolysis in MeOH (10 mL) in the presence of AcOH (0.18 mL, 3.1 mmol), under H_2 atmosphere. The reaction was continued overnight. After that, the reaction mixture was filtered through a short bed of celite and the solution was evaporated under reduced pressure. The saturated aqueous solution of $NaHCO_3$ (30 mL) was added over residue and extracted with Et_2O (3x30 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography using EtOAc:Hexanes (1:19) as an eluent. The product was obtained as colourless oil in 85 % yield. R_f= 0.16 (EtOAc/Hexanes 1:2); $[\alpha]_D^{27}$ = +11.8 (c = 1.45 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 - 7.41 (m, 4H), 7.32 - 7.26 (m, 6H), 4.45 (t, *J* = 7.58 Hz, 1H), 3.74 - 3.71 (m, 1H), 3.07 (s, 3H), 2.60 (dd, *J* = 11.38, 3.50 Hz, 1H), 2.45 (dd, *J* = 11.40, 4.80 Hz, 1H), 2.03 (br, 1H), 1.80 - 1.75 (m, 2H), 0.84 (s, 9H), -0.03 (s, 3H), -0.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.9, 141.6, 129.2, 129.1, 127.7, 127.3, 127.2, 127.0, 85.0, 72.6, 60.7, 55.4, 51.4, 37.6, 25.9, 18.1, -4.7, -4.8; IR (ATR): ν = 3087, 2950, 2928, 2855, 1599, 1492, 1360, 1069 cm^{-1}; HRMS (ESI+) m/z = 398.2537, calcd. for $C_{24}H_{36}NO_2Si$ $[M+H]^+$: 398.2515.



(3*R*,5*S*)-5-(methoxydiphenylmethyl)pyrrolidin-3-ol (9)

To a solution of (2*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-2- (methoxydiphenylmethyl) -pyrrolidine (8b) (0.9 g, 2.3 mmol) in dry THF (38 mL) was added tetra-*n*-

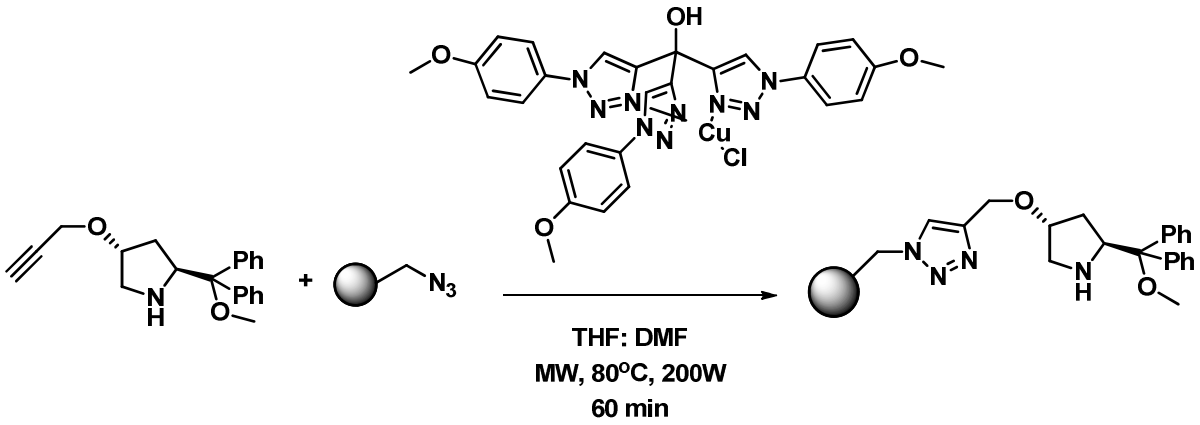
butylammonium fluoride (3 mL, 3 mmol) at 0 ºC under inert atmosphere. Then the mixture was warmed to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted with CH_2Cl_2 (2 x 50 mL). Combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using CH_2Cl_2/MeOH (99:1 to 90:10) as an eluent. The product was obtained as slight yellow solid in 72 % yield. R_f= 0.22 (MeOH/CH_2Cl_2 1:8); $[\alpha]_D^{27}$ = –19.2 (c = 0.92 in MeOH); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 - 7.39 (m, 4H), 7.31 - 7.26 (m, 6H), 4.50 (t, *J* = 15.80 Hz, 1H), 4.01 - 3.98 (m, 1H), 3.07 (s, 3H), 2.71 - 2.67 (m, 1H), 2.49 - 2.45 (br, 2H), 2.34 (dd, *J* = 11.64, 4.24 Hz, 1H), 1.91 - 1.79 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.6, 141.3, 129.2, 128.9, 127.7, 127.5, 127.3, 127.2, 85.1, 72.4, 60.3, 55.0, 51.4, 37.4; IR (ATR): ν = 3343, 3087, 2938, 2826, 1492, 1445, 1073 cm^{-1}; HRMS (ESI+) m/z = 284.1651, calcd. for $C_{18}H_{22}NO_2$ $[M+H]^+$: 284.1651.



(2*S*,4*R*)-2-(methoxydiphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (10)

NaH (124 mg, 60% dispersion in mineral oil) was placed in a flame-dried flask under argon, washed with 2x10 mL portions of dry hexanes and dried. Then dry DMF (5 mL) was added and the mixture cooled to –15 ºC. A solution of (9) (0.44 g, 1.6 mmol) in dry DMF (10 mL) was added to the NaH suspension via cannula. The solution was stirred under inert atmosphere for half an hour, and evolution of H_2 was observed. A solution of 80% propargyl bromide in toluene (0.26 mL, 2.33 mmol) was promptly added and the reaction mixture turned brown colored. The reaction was warmed to 0 ºC and stirred overnight. The reaction was quenched with 5 mL of methanol. Then 100 mL of water were added over the reaction mixture and it was extracted with 3 x 50 mL of CH_2Cl_2. Combined organic layers were dried over $MgSO_4$ and solvent was evaporated under reduced pressure. The product was purified by flash column chromatography using CH_2Cl_2/MeOH (99:1 to

90:10) as eluent. The product was obtained as brown oil in 60% yield. R_f= 0.31 (MeOH/CH_2Cl_2 1:8); $[\alpha]_D^{28}$ = –8.61 (c = 0.45 in CH_2Cl_2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43 - 7.24 (m, 10H), 4.41 (dd, *J* = 7.38, 8.46 Hz, 1H), 4.05 (d, *J* = 2.40 Hz, 2H), 3.82 - 3.78 (m, 1H), 3.07 (s, 3H), 2.86 - 2.82 (m, 1H), 2.41 (dd, *J* = 12.16, 4.56 Hz, 1H), 2.37 (t, *J* = 2.42 Hz, 1H), 2.02 - 1.96 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.9, 141.5, 129.9, 129.2, 129.0, 128.3, 127.7, 127.3, 127.2, 127.1, 84.9, 80.1, 79.5, 74.0, 60.8, 56.1, 52.1, 51.5, 34.0; IR (ATR): ν = 3286, 3087, 2935, 2855, 2113, 1658, 1596, 1491, 1444, 1072 cm^{-1}. HRMS (ESI+) m/z = 322.1796, calcd. for $C_{21}H_{23}NO_2$ $(M+H)^+$: 322.1807.



4-((((3*R*,5*S*)-5-(methoxydiphenylmethyl)pyrrolidin-3-yl)oxy)methyl)-1-methyl-1*H*-1,2,3-triazole polystyrene (11)

(2*S*,4*R*)-2-(methoxydiphenylmethyl)-4-(prop-2-yn-1-yloxy)pyrrolidine (10) (122 mg, 0.38 mmol), azidomethylpolystyrene resin [4] (610 mg, *f* = 0.517 mmol g^{-1}), 3 mL of DMF, 3 mL of THF and *tris*(1-(4-methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methanol·CuCl catalyst[5] (20.5 mg, 0.03 mmol, 10 mol %) were placed in a tube for microwave reactor. The reaction mixture was heated at 80 ºC for 50 min under microwave irradiation of 200 W without stirring. After the reaction was completed, the resin was filtered and washed with CH_2Cl_2 (200 mL) and THF (200 mL) and was dried overnight in vacuo at 40 ºC. IR (ATR): ν = 3082, 3059, 2918, 1600, 1492, 1451, 1265, 1248, 1066 cm^{-1}; A 99% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.52; found: C 88.06, H 7.41, N 2.48; *f* = 0.443 mmol g^{-1}.

3. References for the Supporting Information:

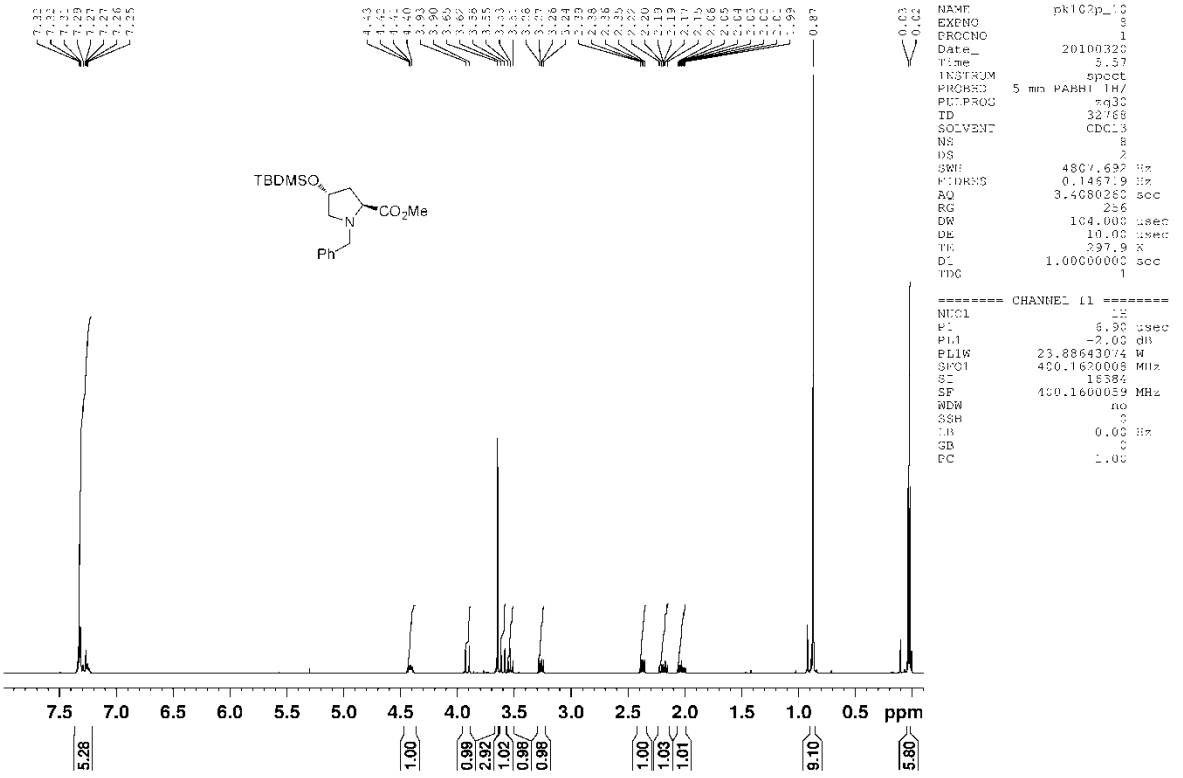
[1] Yield of incorporation calculated as 100*f*/*f*max, in which *f* (mmol ligand per gram resin) is the fuctionalization calculated from the nitrogen elemental analysis, and *f*max (mmol ligand per gram resin), the maximal ligand functionalization level, is calculated as described in the following: Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. K. M. *J. Org. Chem.* **1998**, *63*, 6309.

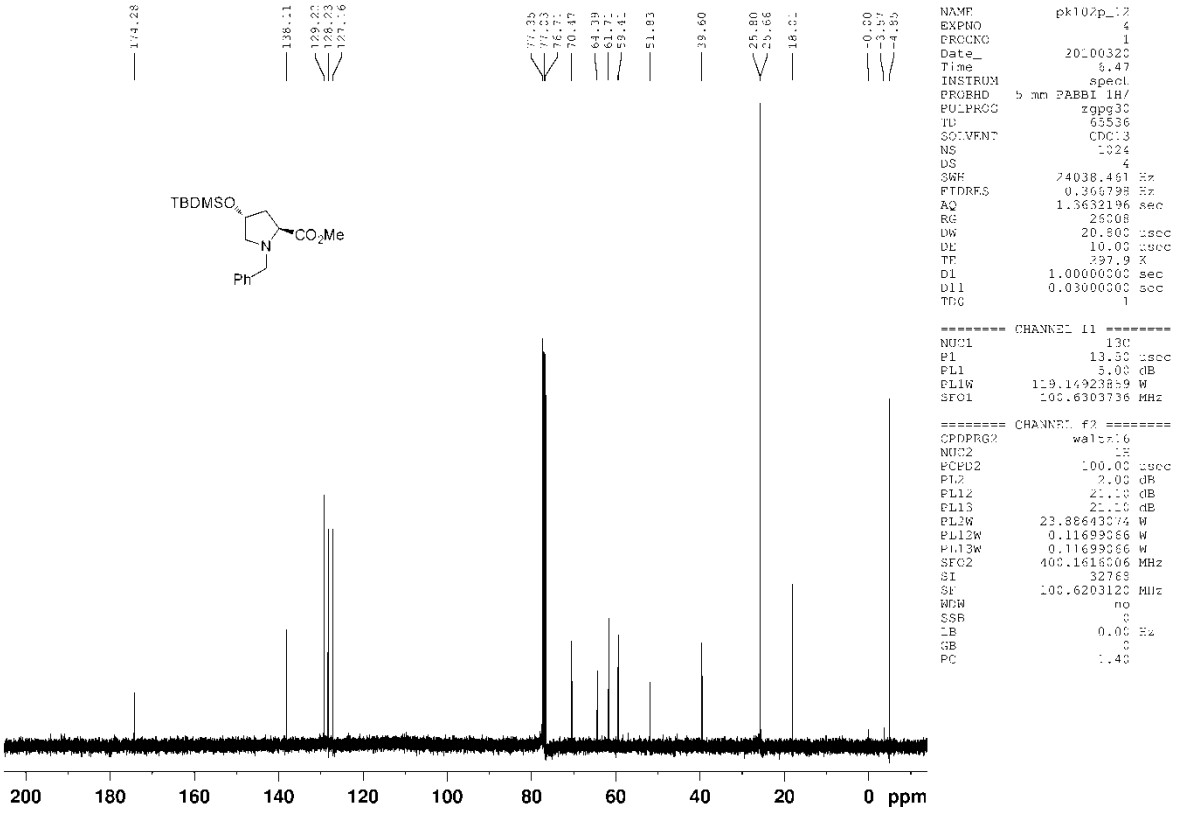
[2] Rosen, T; Fesik, S. W.; Chu, D. T. W.; Pernet, A. G. *Synthesis* **1988**, *1*, 40.

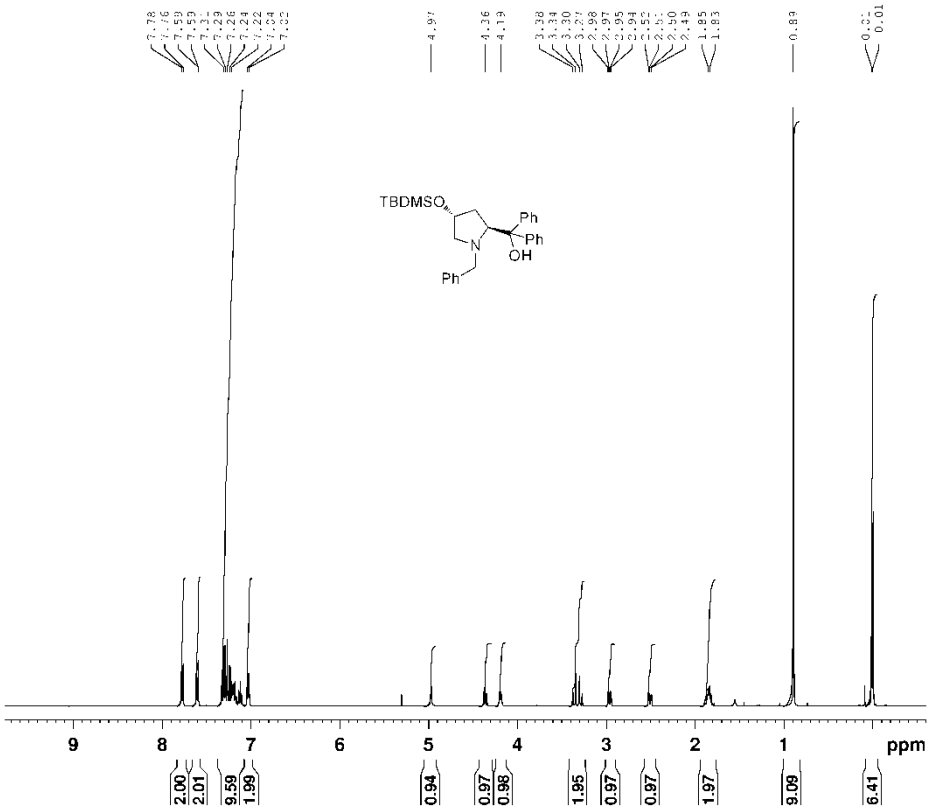
[3] Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; and Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1598.

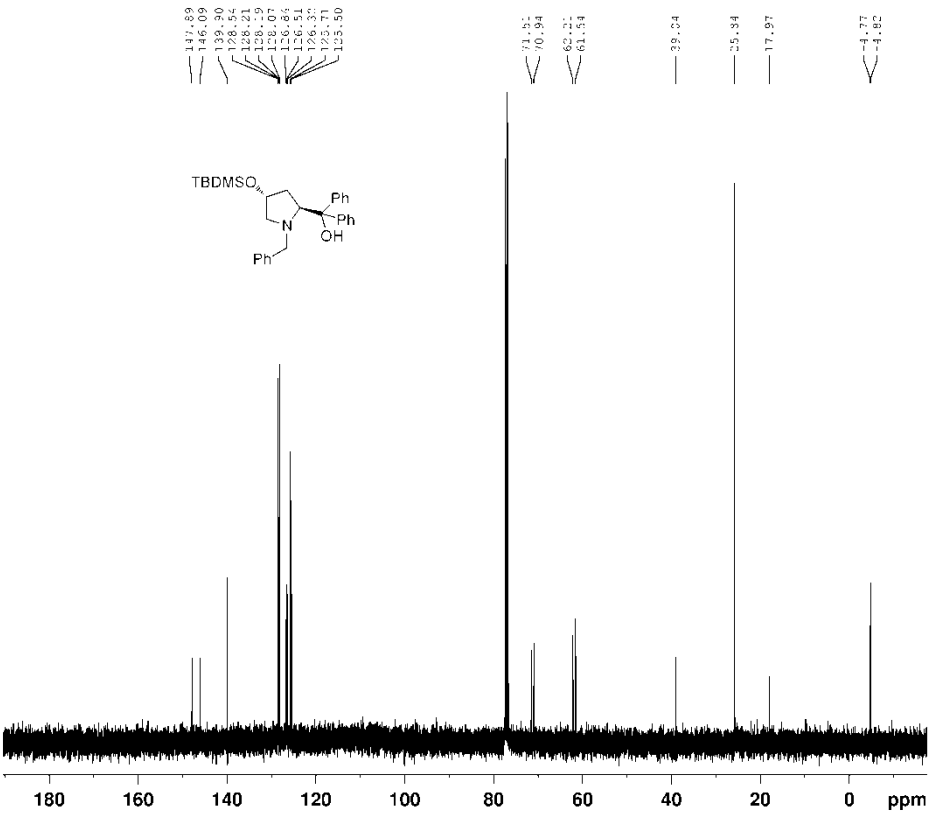
[4] Font, D.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2006**, *8*, 4653

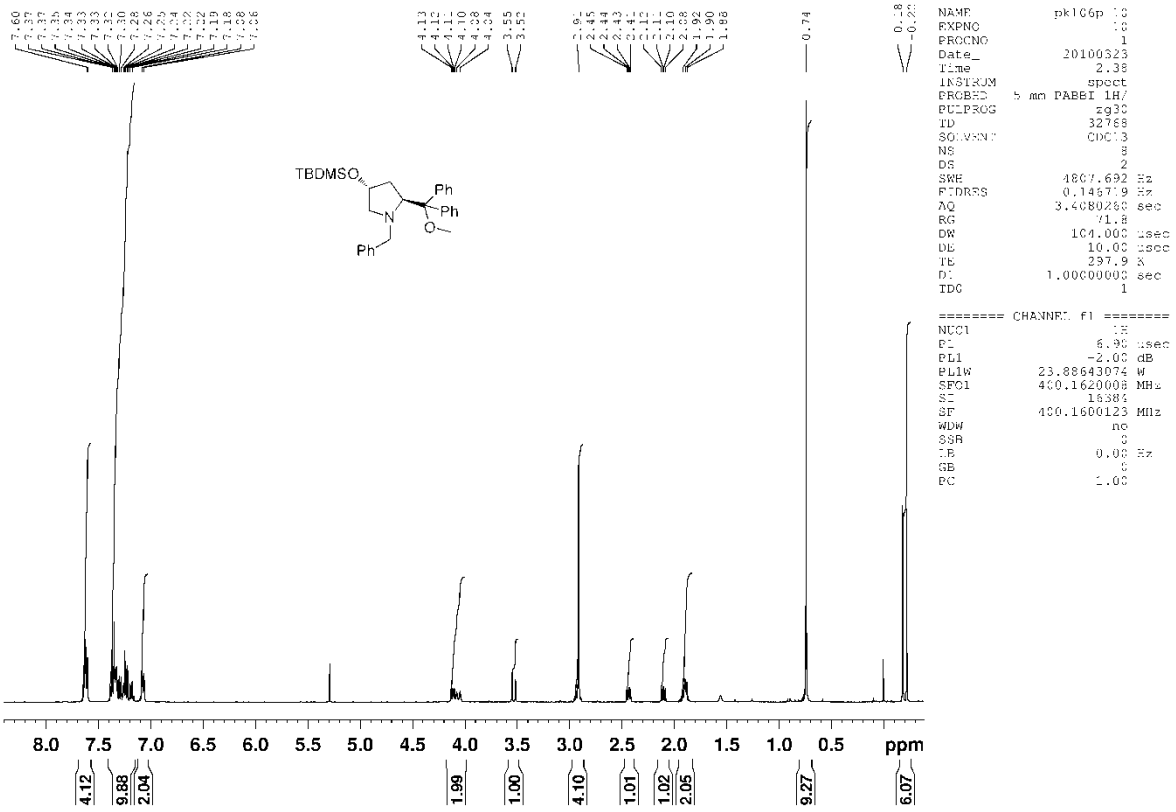
[5] Özcubukcu, S.; Ozkal, E.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2009**, *11*, 4680

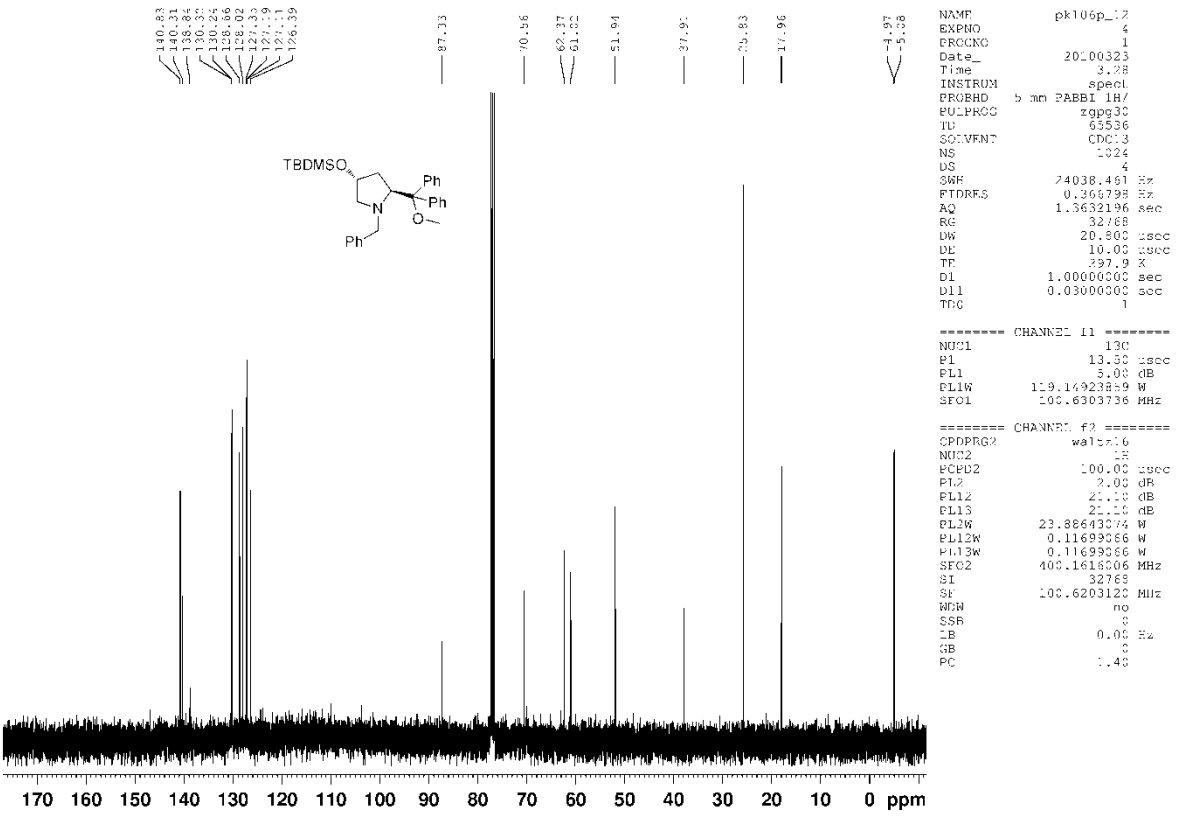


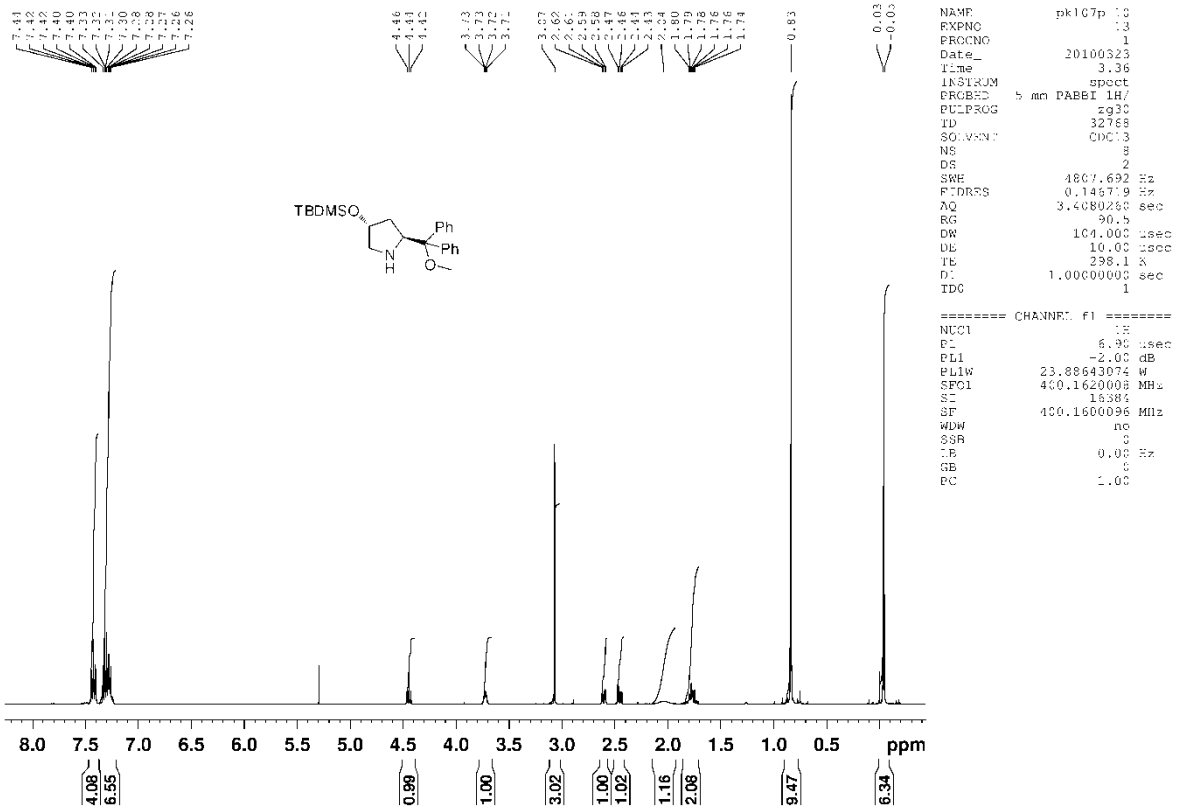


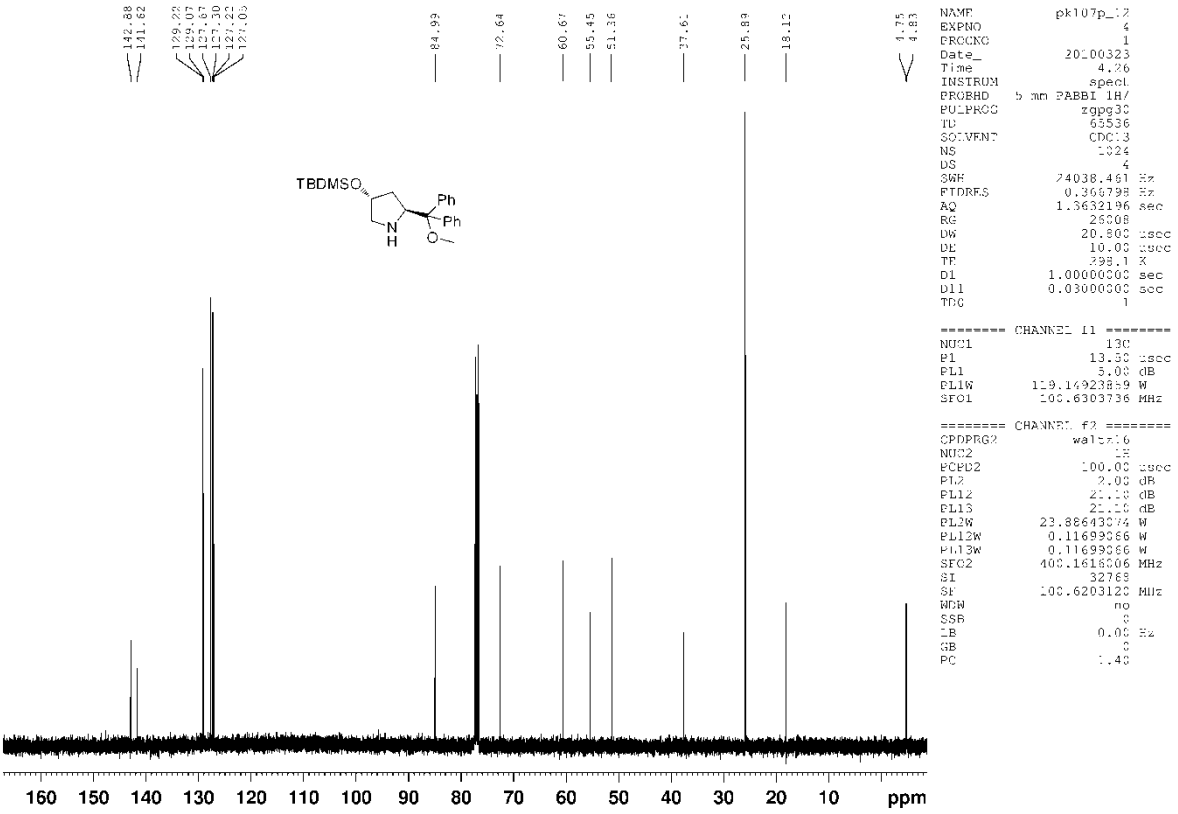


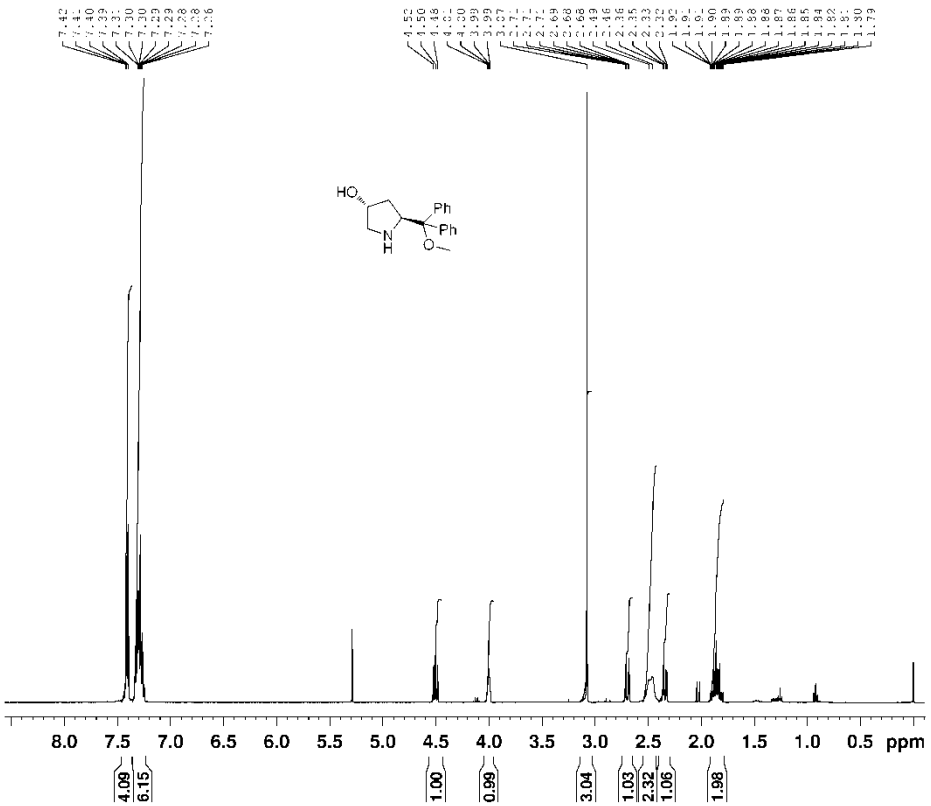










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D1            1.00000000 sec
TD0                   1

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PL1               -2.00 dB
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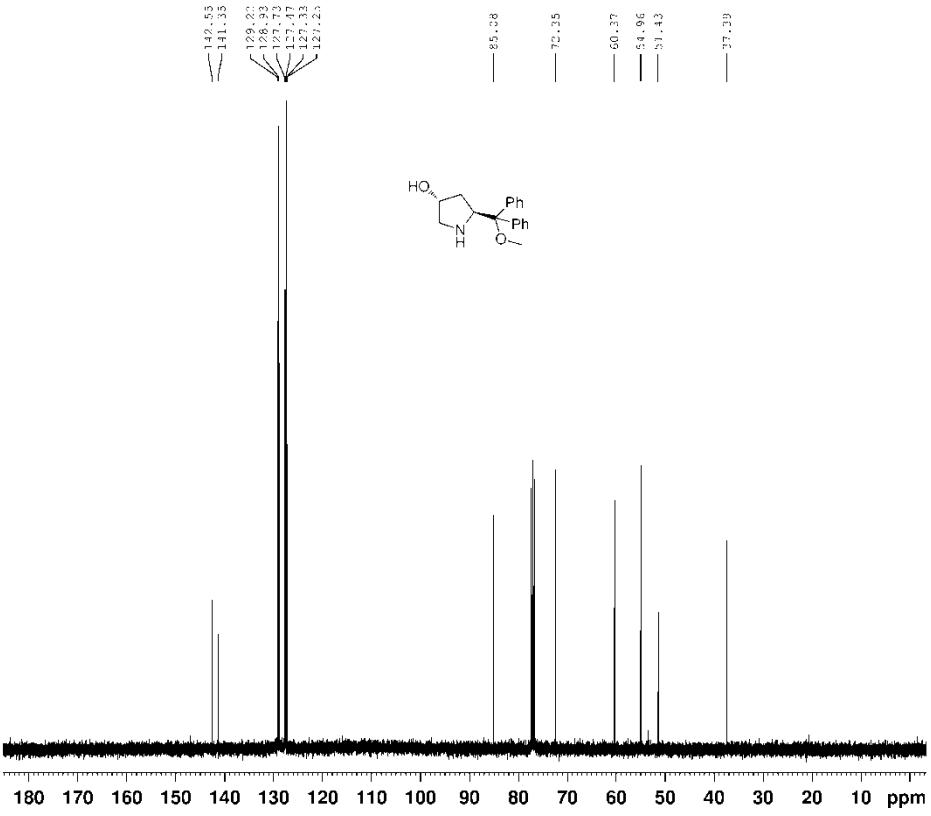


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DE                10.00 usec
TE                297.9 K
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D11           0.03000000 sec
TD0                   1

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PL13              21.18 dB
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PL12W        0.11699866 W
PL13W        0.11699866 W
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SI                32768
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WDW                  no
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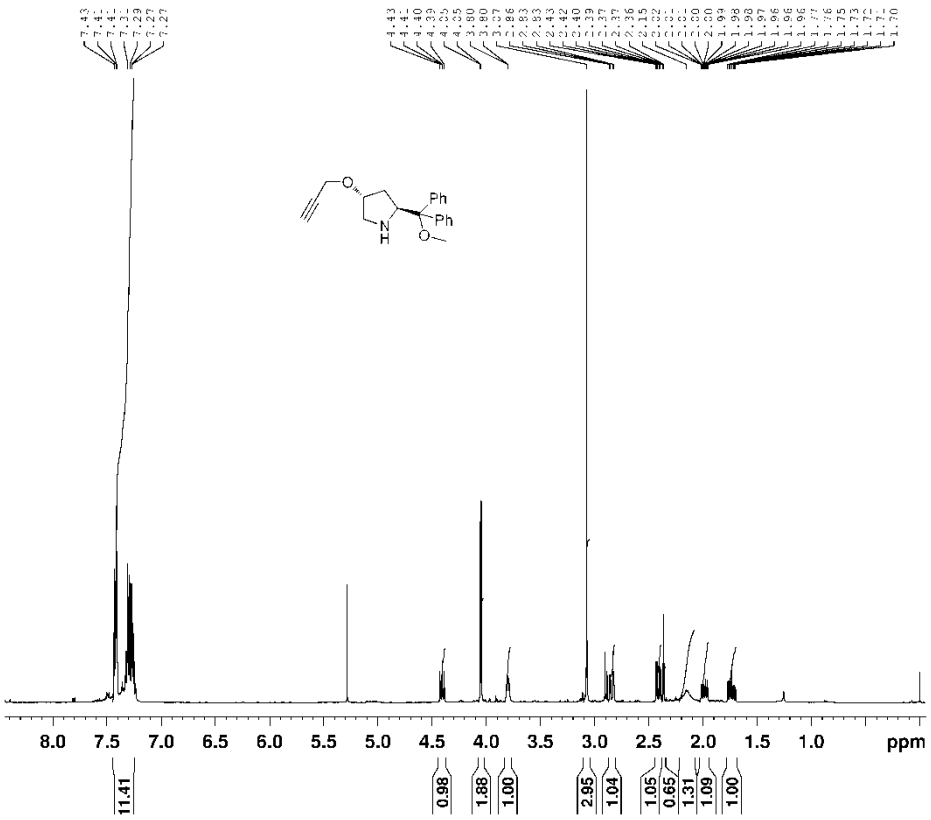


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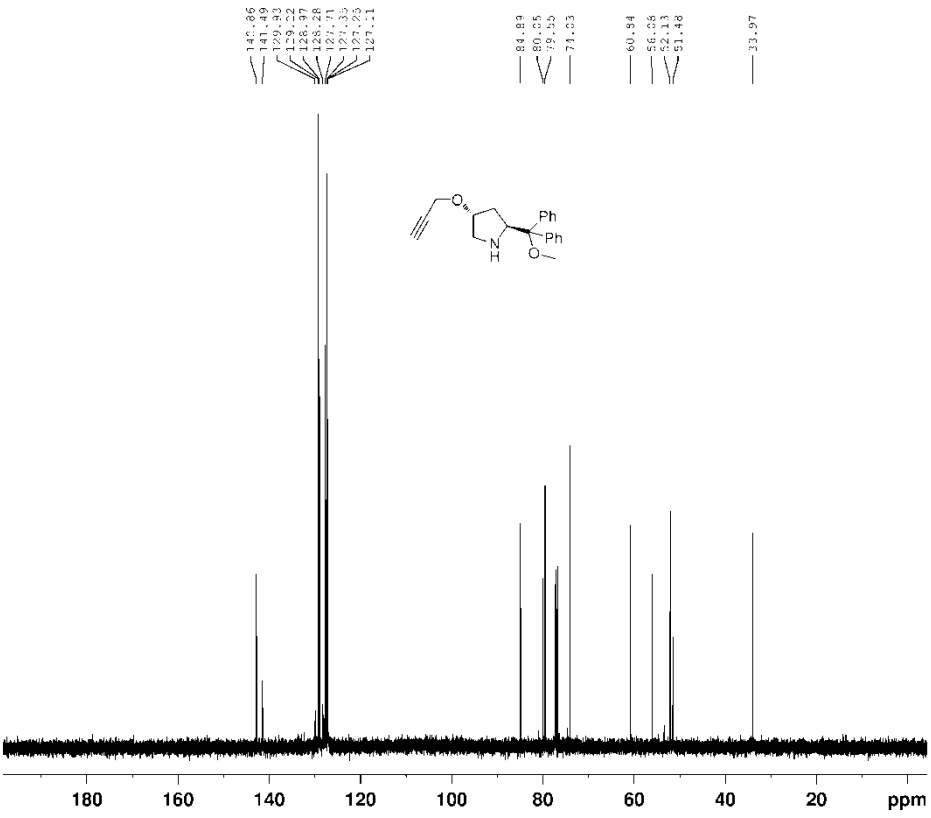


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DS                     4
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FIDRES        0.366798 Hz
AQ            1.3632196 sec
RG              20642.5
DW                20.800 usec
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D1            1.00000000 sec
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TD0                    1

======== CHANNEL f1 ========
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SFO1        100.6303736 MHz

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PL13W        0.11699066 W
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SI                 32768
SF          100.6203123 MHz
WDW                   no
SSB                    0
LB                  0.00 Hz
GB                     0
PC                  1.40
```

CHAPTER III

3. PYRROLIDINE BASED BIFUNCTIONAL THIOUREA ORGANOCATALYSTS IN *anti*-MANNICH REACTION

3.1. (THIO)UREA ORGANOCATALYSTS

Organocatalysts are one prominent but still developing branch of asymmetric catalysis. Proline and its derivatives are early examples of powerful organocatalysts for enamine and iminium-ion activation chemistry but, more or less in same period, another organocatalytic activation mode, H-bonding, was introduced. H-bonding organocatalysts are LUMO lowering activation catalysts which act by sharing of a hydrogen atom with the substrate.[1] (Thio)urea-based organocatalysts have become the leading examples of this new activation mode with the efforts of Jacobsen and co-workers.[2] Following chiral ureas, thioureas, amidinium or guanidinium ions, squaramides, and diols became the most widely used catalysts acting through this type of activation.

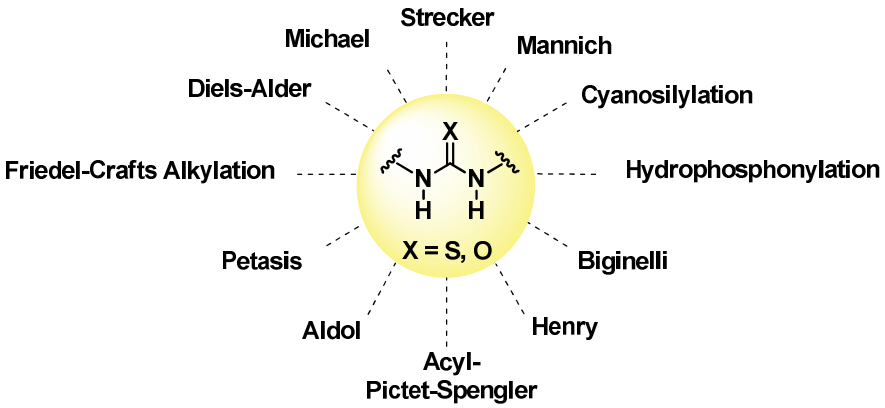

Figure 3.1. (Thio)urea-catalyzed reactions.

As most of the other H-bonding organocatalysts, urea and thiourea analogues are used in many different transformations efficiently (Figure 3.1), such as the activation of carbonyl compounds,[3] imines,[2a] and in the stabilization of the

[1] Ríos Torres, R. *Stereoselective Organocatalysis: Bond Formation Methodologies and Activation Modes*, *John Wiley & Sons, Inc*. **2013.**
[2] a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1998**, *120*, 4901-4902. b) Vachal, P.; Jacobsen, E. N. *Org. Lett*. **2000**, *2*, 867-870. c) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed*. **2000**, *39*, 1279-1281. d) Su, J. T.; Vachal, P.; Jacobsen, E. N. *Adv. Synth. Catal*. **2001**, *343*, 197-200. e) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 10012-10014. f) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2002**, *124*, 12964-12965.
[3] a) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N.; Lex, J. *Angew. Chem., Int. Ed*. **2005**, *44*, 807-811. b) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N.; Lex, J. *Chem. Commun*. **2005**, 1898-1900. c) Vakulya, B.; Varga, S.; Csampai, A.; Soós, T. *Org. Lett*. **2005**, *7*, 1967-1969. d) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2005**, *127*, 8964-8965.

transition state of cycloaddition reactions,[4] Claisen rearrangements,[5] and Michael reactions.[6] At the same time, many studies have been done, especially on the activation of nitro and carbonyl groups by H-bonding interaction (Figure 3.2 a).[4a,b,7]

Studies carried out with urea and thiourea organocatalysts have shown that thioureas are more active catalysts then ureas. This reactivity difference can be explained in different aspects. For instance, it has been found that thioureas are more acidic than ureas.[8] In addition, the sulfur atom in thiourea as compared to the oxygen atom in urea has lower electronegativity,[9] which is an important feature to decrease the possibility of self-association in molecules. Additionally, thioureas are more soluble in organic solvents.[10] However, the preference of catalyst selection depends on each specific reaction.

After the first use of a peptide-thiourea catalyst in the enantioselective Strecker reaction by Jacobsen *et al.,*[2a] many different (thio)urea organocatalysts were designed and synthesized, mainly varying in chiral scaffold (Figure 3.2 b). The addition of a Brønsted basic moiety to the H-bonding (thio)urea unit brought a new catalyst type which is called bifunctional (thio)urea organocatalysts. The principle behind this bifunctional catalyst was activating both electrophile and nucleophile within the same catalyst by possessing both Brønsted basic and Lewis acidic parts. On the other hand, there are some exceptions to this general activation mode of bifunctional (thio)urea organocatalysts in which the (thio)urea motif can bind to an anion or cation.[11]

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[4] a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217-220. b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407-414. c) Liu, Y. K.; Liu, H.; Du, W.; Yue, L.; Chen, Y. C. *Chem. Eur. J.* **2008**, *14*, 9873-9877. d) Kramer, C. S.; Bräse, S. *Beilstein J. Org. Chem.* **2013**, *9*, 1414-1418

[5] a) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2008**, *130*, 9228-9229. b) Uyeda, C.; Rötheli, A. R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 9753-9756. c) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062-5075.

[6] a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672-12673. b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 119-125.

[7] a) Curran, D. P.; Kou, L. H. *J. Org. Chem.* **1994**, *59*, 3259-3261. b) Curran, D. P.; Kou, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647-6650. c) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289-296. d) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817-2821. e) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301-1305.

[8] a) Bordwell, F. G.; Algrim, D. J; Harrelson Jr., J. A. *J. Am. Chem. Soc*. **1988**, *110*, 5903-5904. b) Jakab, G.; Tancon, C.; Zhang, Z.; Lippert, K. M.; Schreiner, P. R. *Org. Lett*. **2012**, *14*, 1724-1727.

[9] Dannecker, W.; Kopf, J.; Rust, H. *Cryst. Struct. Commun*. **1979**, *8*, 429-432.

[10] Curran, D. P.; Kuo, L. H. *Tetrahedron Lett*. **1995**, *36*, 6647-6650.

[11] a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404-13405. b) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2008**, *130*, 7198-7199. c) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2009**, *131*, 15358-15374. d) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968-970.

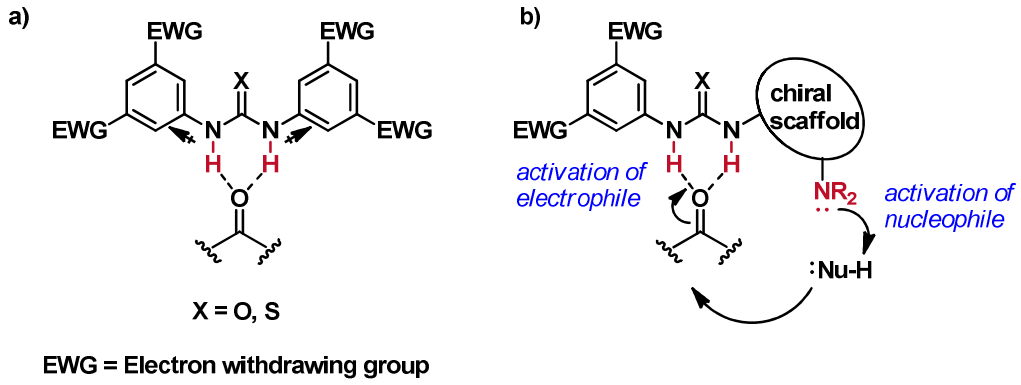
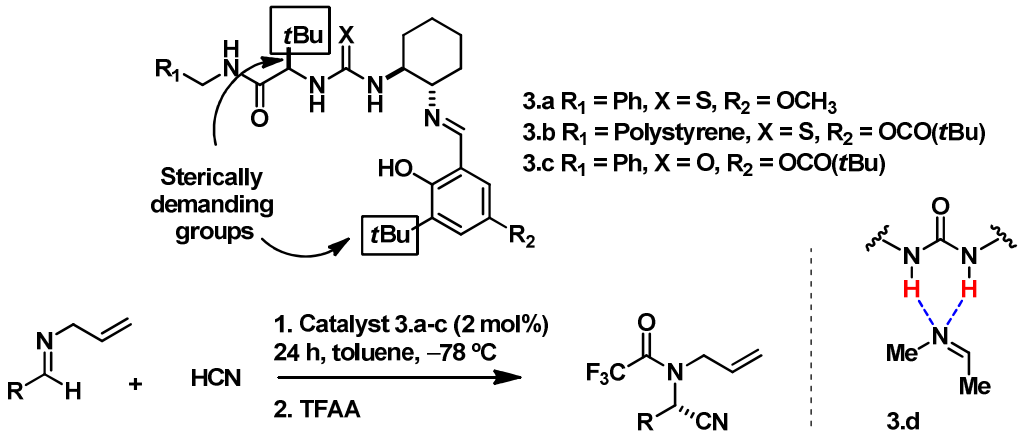


Figure 3.2. a) H-bonding organocatalysts general structure b) General structure of bifunctional (thio)urea organocatalysts.

3.2. (THIO)UREA-CATALYZED ASYMMETRIC REACTIONS

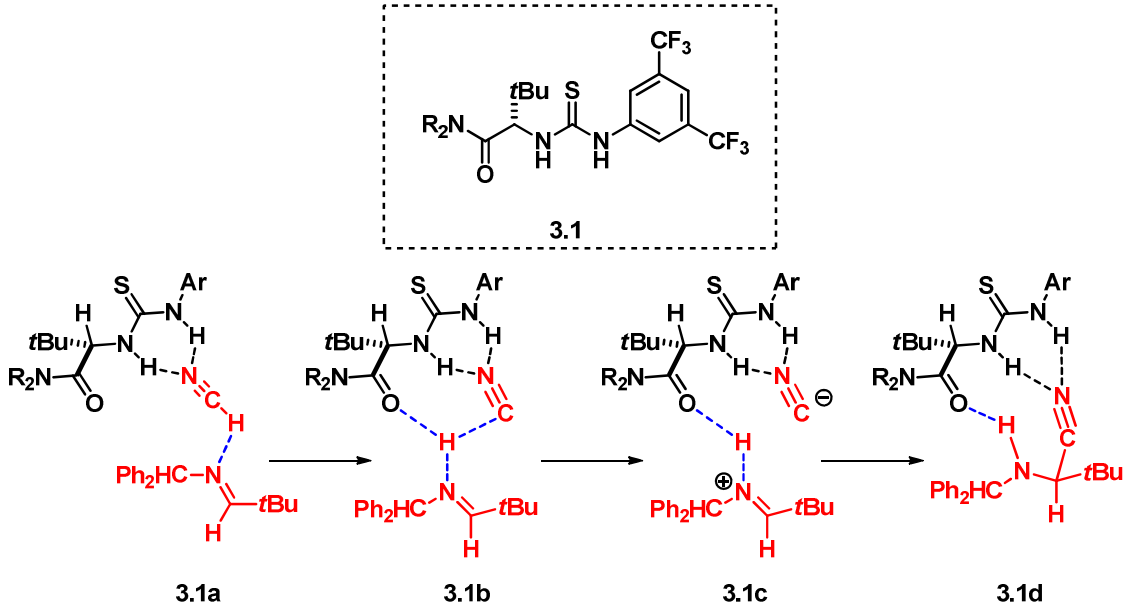
The initial examples from the Jacobsen group took place with the peptide derived (thio)urea Schiff base homogeneous (**3.a-c**) and heterogeneous (**3.b**) catalysts. They used these catalysts in the asymmetric hydrocyanation of aromatic imines (Scheme 3.1),[2] and they obtained the corresponding α-amino acid derivatives in high yields and enantiomeric excesses. According to their preliminary mechanistic analysis they found that the urea functionality **3.d** was responsible for catalytic activity by interacting with the imine substrate via H-bonding. However, reaction conditions were not satisfactory since the scale-up synthesis of α-amino acid derivatives with those catalysts was not possible.



Scheme 3.1. (Thio)urea-catalyzed Strecker reaction developed by Jacobsen *et al.*

Since then, Jacobsen and co-workers have designed new catalysts by using their experience on the subject. They discovered that amido-thiourea catalysts **3.1** which do not bear a cyclohexanediamino moiety are more active catalysts.[11c,d] The use of newly designed catalysts improved the reaction

conditions: no cryogenic temperatures were required and also the hazardous cyanide source was changed to an inexpensive and easy to handle cyanide salt. At the same time, by the help of mechanistic studies it was found that the addition of HCN to imines proceeds through catalyst-bound cyanide/iminium ion. First, the thiourea binds to the HCN Lewis basic nitrogen and then transfers its acidic proton to the imine (**3.1a**). The newly formed species **3.1a** then undergoes a rearrangement to give separate charged species. The N-H of the imine is transferred from the bound cyanide to the carbonyl of the amide in catalyst (**3.1b**). Then this charge separated intermediate **3.1c** collapses to form the α-amino nitrile product **3.1d** (Scheme 3.2).[12]

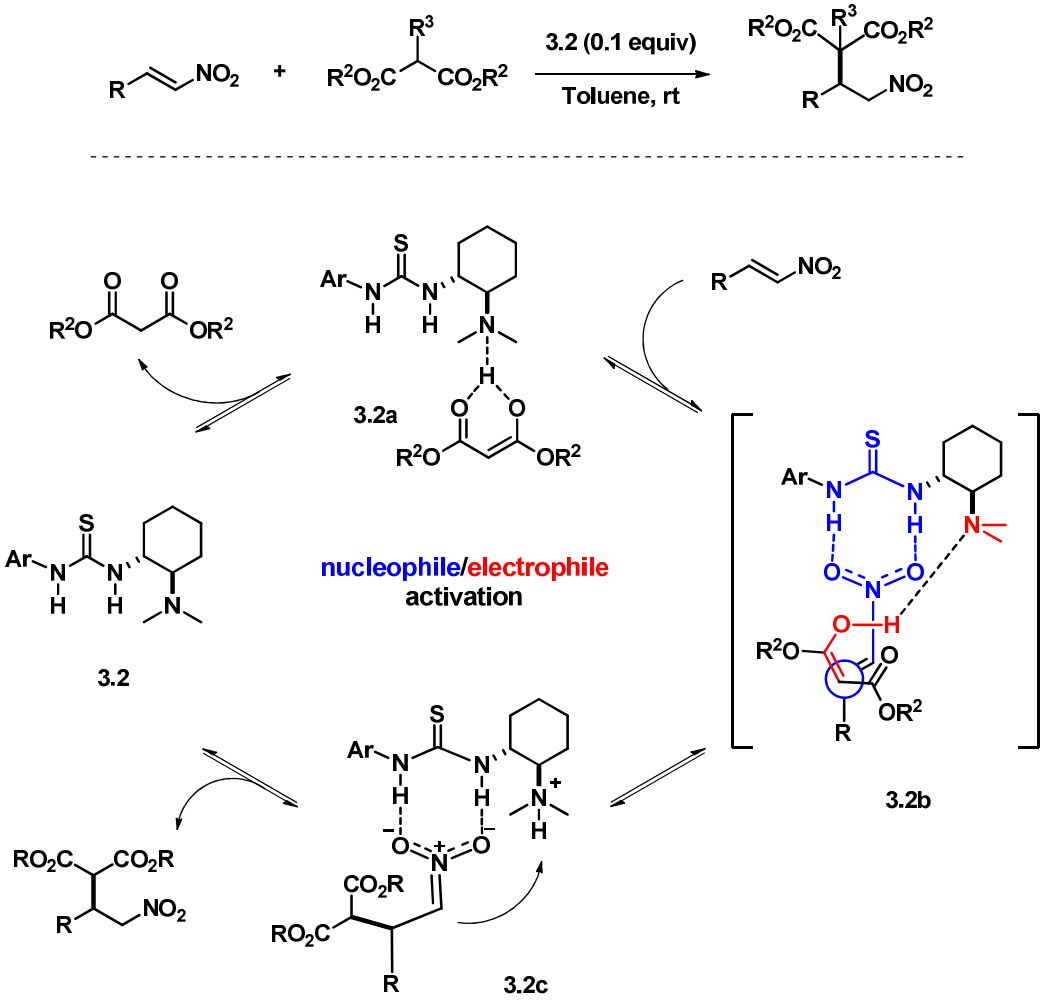


Scheme 3.2. Proposed mechanism for the thiourea-catalyzed Strecker reaction.

After Jacobsen's initial peptide derived catalysts, the first bifunctional thiourea tertiary amine organocatalyst (**3.2**) has been used in the conjugate addition reaction of malonates to nitroolefins by Takemoto and coworkers. It has been explained that this additional basic site is necessary for the activation of the nucleophile, while the catalyst simultaneously activates the nitroolefin and the malonate to form the product with high enantioselectivity.[6a] Then, after a detailed analysis, the following reaction mechanism was proposed (Scheme 3.3). The first step is the deprotonation of malonate by basic tertiary amine group **3.2a**. After that, the nitroolefin interacts with this complex through H-bonding (**3.2b**) and a

[12] Knowles, R. R.; Jacobsen, E. N. *Proc. Nat. Acad. Sci.* **2010**, *107*, 20678-20685.

nitronate complex **3.2c** is formed. The last step is the abstraction of a proton from the amino group of the catalyst by nitronate and the catalyst is released with the desired product formation.[6b]



Scheme 3.3. Thiourea-catalyzed Michael addition of malonates to nitroolefins (R^3 is omitted for clarity).

In 2005, *cinchona* derived bifunctional thiourea organocatalysts were introduced independently by the Connon, Dixon and Soós groups.[3c,13] They developed a new mode of action for *cinchona* organocatalysts by incorporating a thiourea motif and those catalysts were initially used in conjugate addition reaction. Similarly to Takemoto's catalyst, the thiourea motif binds to the electrophile and the quinuclidine ring activates the nucleophilic substrate (Figure

[13] a) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367-6370. b) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 35, 4481-4483.

3.3). After that, *cinchona* derived bifunctional thiourea organocatalysts have been used in many other transformations.[14]

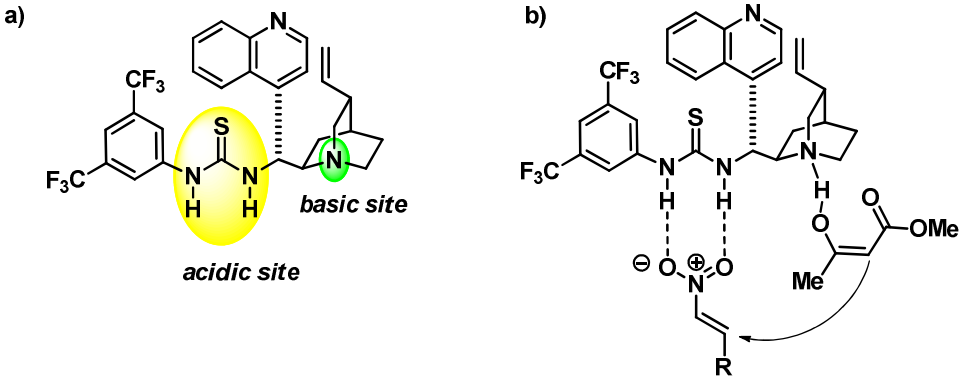
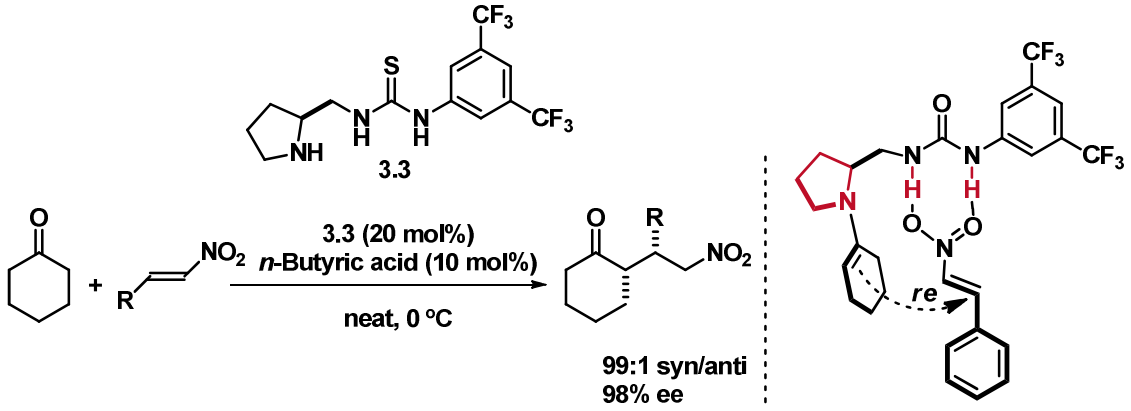


Figure 3.3. a) General structure of Connon, Dixon, Soós catalyst. b) General mode of activation.

In 2006, the Tang group designed a pyrrolidine (thio)urea organocatalyst to combine the advantages of proline derived catalysts with H-bonding catalysts.[15] The catalyst was used in the asymmetric Michael addition of cyclohexanone to nitroolefins and resulted in high yields, diastereoselectivities and enantioselectivities. Presumably, the activity of the catalytst was due to the reactive enamine species which is formed upon condensation of the pyrrolidine with the carbonyl compound, while the urea activates the nitroolefin through H-bonding for site selective nucleophilic attack (Scheme 3.4).



Scheme 3.4. Pyrrolidine-thiourea bifunctional organocatalyst in the Michael addition of cyclohexanone to nitroolefins.

[14] a) Wang, Y.Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156-8157. b) Bode, C. M.; Ting A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499-11505. c) Wang, Y.; Li, H.; Wang, Y.Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364-6365. d) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929-931. e) Amere, M.; Lasne M. C.; Rouden, J. *Org. Lett.* **2007**, *9*, 2621-2624. f) Connon, S. J. *Chem. Commun*. **2008**, 22, 2499-2510. g) Xi, Y.; Shi, X. *Chem. Commun*. **2013**, *49*, 8583-8585.

[15] Cao, C. L.; Ye, M. C.; Sun, X. L.; Tang, Y. *Org. Lett*. **2006**, *8*, 2901-2904.

Pyrrolidine derived thiourea organocatalysts have been used in Michael addition reactions by other research groups as well.[16] In the literature, apart from Michael addition, these organocatalysts have only been used in the α-chlorination of aldehydes[17] and enantioselective *anti*-Mannich reactions[18] (Figure 3.4).

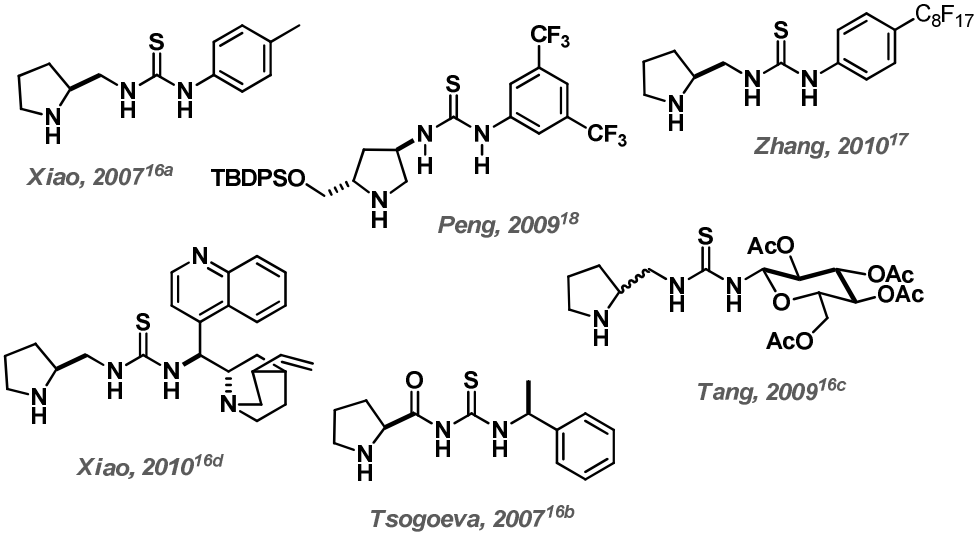


Figure 3.4. Examples of pyrrolidine based-thiourea bifunctional organocatalysts used in literature.

Overall, in this study, we wanted to use our previous experience on pyrrolidine based *anti*-Mannich catalysts, which are obtained from desymmetrization of *meso*-*N*-trifluoroacetyl-3-pyrroline oxide (Figure 3.5).[19] By combining this enantiopure pyrrolidine intermediate with hydrogen bonding thiourea motif, new pyrrolidine based thiourea organocatalyst were synthesized to be evaluated in the *anti*-selective Mannich reaction.

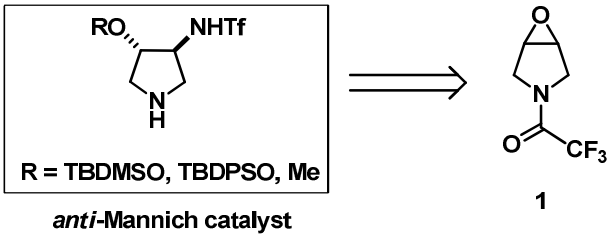


Figure 3.5. Pericàs group pyrrolidine-based *anti*-selective catalysts for the Mannich reaction.

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[16] a) Cao, Y. J.; Lai, Y. Y.; Wang, X.; Lia, Y. J.; Xiao, W. J. *Tetrahedron Lett.* **2007**, *48*, 21-24. b) Wei, S.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catalysis Today* **2007**, *121*, 151-157. c) Lu, A.; Gao, P.; Wu, Y.; Wang, Y.; Zhou, Z.; Tang, C. *Org. Biomol. Chem.* **2009**, *7*, 3141-3147. d) Chen, J. R.; Cao, Y. J.; Zou, Y. Q.; Tan, F.; Fu, L.; Zhu, X. Y.; Xiao, W. J. *Org. Biomol. Chem.* **2010**, *8*, 1275-1279.
[17] Wang, L.; Cai, C.; Curran D. P.; Zhang, W. *Synlett* **2010**, *3*, 433-436.
[18] Zhang, H.; Chuan, Y.; Li, Z.; Peng, Y. *Adv. Synth. Catal*. **2009**, *351*, 2288-2294.
[19] Martín-Rapún, R.; Fan, X.; Sayalero, S.; Bahramnejad, M.; Cuevas, F.; Pericàs, M. A. *Chem. Eur. J.* **2011**, *17*, 8780-8783.

3.2.1. Thiourea-Catalyzed Mannich Reactions

Asymmetric Mannich reactions are versatile and effective carbon-carbon bond forming reactions. For the synthesis of β-amino carbonyl compounds, Mannich is a previously used efficient reaction and several organocatalytic systems have been described for these transformations.[20] This reaction was introduced for the first time by Carl Mannich in 1912. He performed the condensation of formaldehyde with ammonia to form the iminium ion and then with the subsequent addition of a carbon nucleophile a Mannich product was formed.[21] The first enantioselective organocatalytic example was shown by List et al. in 2000, using L-Proline,[22] and shortly after Jacobsen and co-workers developed a (thio)urea catalyzed Mannich reaction.[23] They performed the enantioselective addition of silyl ketene acetals to *N*-Boc-aldimines taking advantage of their initial experience on imine activation via H-bonding (thio)urea.

In the literature, many successful examples of organocatalytic *syn*-selective Mannich reactions[24] have been published; however, *anti*-selective Mannich reactions[25] are less explored and considered to be more challenging. According to previous attempts, it has been found that pyrrolidine-based catalysts are more reactive in *anti*-Mannich reaction of unmodified aldehydes and ketones.[25b,c]

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[22] List, B. *J. Am. Chem. Soc*. **2000**, *122*, 9336-9337.

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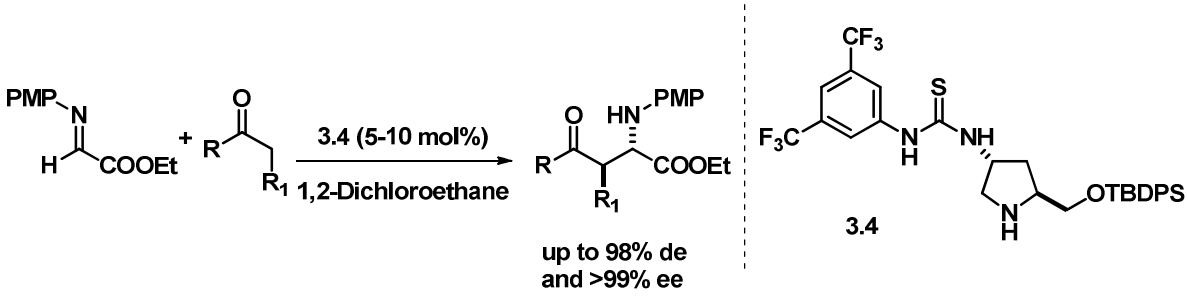
[24] a) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc*. **2002**, *124*, 827-833. b) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1842-1843. c) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas III, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 1866-1867. d) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed*. **2003**, *42*, 3677-3680. e) Ibrahem, I.; Casas, J.; Córdova, A. *Angew. Chem., Int. Ed*. **2004**, *43*, 6528-6531. f) Westermann, B.; Neuhaus, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4077-4079. g) Yang, J. W.; Stadler, M.; List, B. *Angew. Chem., Int. Ed*. **2007**, *46*, 609-611. h) Hayashi, Y.; Urushima, T.; Aratake, S.; Okano, T.; Obi, K. *Org. Lett*. **2008**, *10*, 21-24. i) Kano, T.; Sakamoto, R.; Akakura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 7516-7520.

[25] a) Córdova, A.; Barbas III, C. F. *Tetrahedron Lett.* **2002**, *43*, 7749-7752. b) Mitsumori, S.; Zhang, H.; Cheong, P. H. Y.; Houk, K. N.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc.* **2006**, *128*, 1040-1041. c) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas III, C. F. *J. Am. Chem. Soc*. **2006**, *128*, 9630-9631. d) Wang, C. J.; Dong, X. Q.; Zhang, Z. H.; Xue, Z. Y.; Teng, H. L. *J. Am. Chem. Soc*. **2008**, *130*, 8606-8607. e) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1838-1840. f) Zhang, H.; Chuan, Y.; Li, Z.; Peng, Y. *Adv. Synth. Catal.* **2009**, *351*, 2288-2294. g) Chuan, Y. M.; Chen, G. H.; Gao, J. Z.; Zhang, H.; Peng, Y. *Chem. Commun*. **2011**, *47*, 3260-3262.

For thiourea-based organocatalysts, *anti*-Mannich product formation was first reported by Tsogoeva *et al.*[26] They used a primary amine catalyst for the simple Mannich type addition of unmodified ketones to *N*-benzoylhydrazones, which proceeded with good yields and enantioselectivities. Interestingly, they found that when acyclic ketones were used, *anti*-Mannich products were obtained whereas cyclic ketones gave rise to the *syn*-product. Based on their mechanistic studies, they proposed that both the enol and enamine mechanisms might be involved in this primary amine-thiourea-catalyzed Mannich-type reaction.

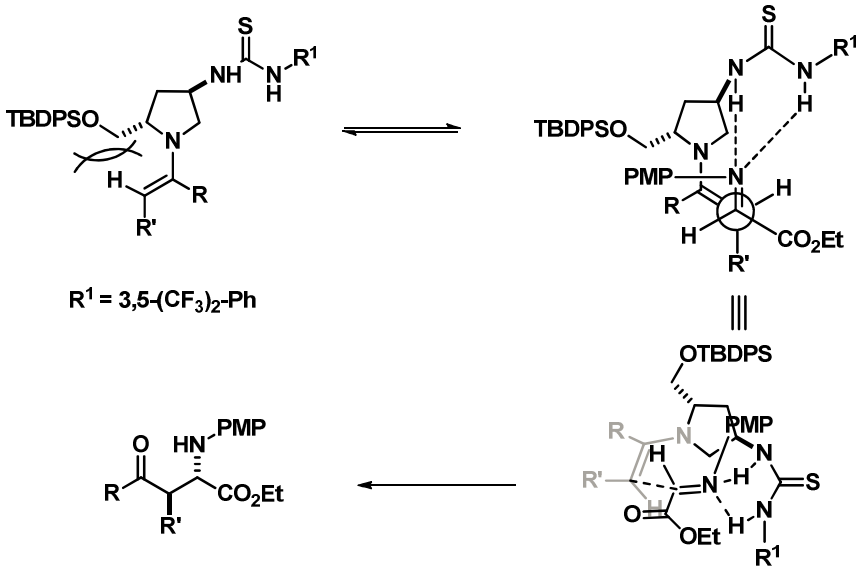
Afterwards, Peng *et al.* developed a pyrrolidine-based secondary amine thiourea organocatalyst **3.4** for the enantioselective *anti*-Mannich reaction.[25f] The simple Mannich type addition of unmodified aldehydes and ketones to *N*-*p*-methoxyphenyl (PMP)-protected α-iminoglyoxylate took place with very high diastereoselectivities and enantioselectivities (Scheme 3.5). During catalyst screening, they found that for high reactivity and enantioselectivity, it is crucial to have an acidic H-bond donating functionality; in addition, for high diastereoselectivity, a face shielding bulky group on catalyst is a must. Finally, the optimized catalyst **3.4** has a proton donor thiourea group at 4-position and a bulky group at α-position of the pyrrolidine ring.



Scheme 3.5. Pyrrolidine-based thiourea organocatalysts developed by Peng group and *anti*-Mannich-type reaction of unmodified aldehydes and ketones.

The possible reason of high stereoselectivity was observed in these tentatively reactions was explained using the transition state model proposed by Barbas.[25b] The bulky (-CH_2OTBDPS) group shields the *re*-face of the enamine and favors the possible attack from the *si*-face. Also, the H-bonding unit activates the imine and stabilizes the transition state (Scheme 3.6).

[26] Yalalov, D. A.; Tsogoeva, S. B.; Shubina, T. E.; Martynova, I. M.; Clark, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 6624-6628.



Scheme 3.6. Proposed transition state by Peng *et al.*

3.3. AIM OF OUR STUDY

Based on a similar work for the synthesis of β-amino carbonyl compounds[25f] and our research group's previous results,[19] we decided to develop our own pyrrolidine-based thiourea organocatalyst for *anti*-Mannich reactions. According to previously published studies, the active catalyst should have a H-bond donating group and a pyrrolidine ring for the activation of electrophiles and nucleophiles. Respectively pyrrolidine-based thiourea organocatalysts designed by our group have similar functional groups but in different positions on the ring, so we decided to study the importance of the substitution pattern on the catalytic activity and the selectivity.

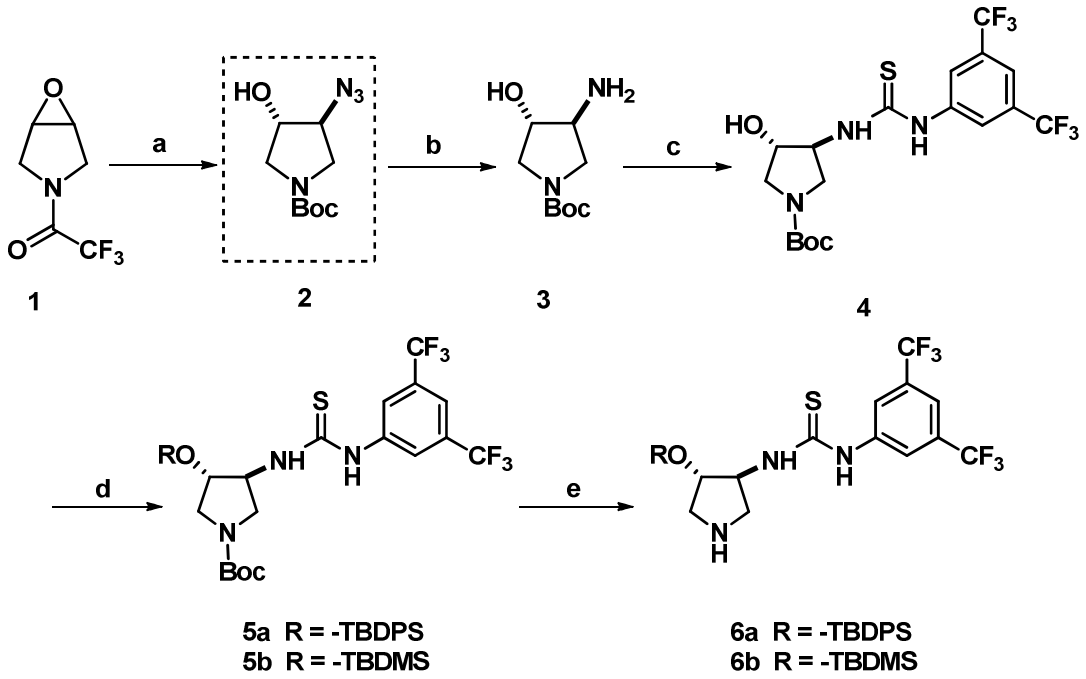
3.4. RESULTS AND DISCUSSION

3.4.1. Pyrrolidine-based Thiourea Organocatalysts

Preparation

Catalysts **6a** and **6b** were readily prepared through the key intermediate **2**, which was obtained from the desymmetrization of *meso*-*N*-trifluoroacetyl-3-pyrroline oxide through the sequences shown in Scheme 3.7. First asymmetric ring-opening of *N*-trifluoroacetyl-3-pyrroline oxide with $TMSN_3$ catalyzed by (*R*,*R*)-(salen)Cr^{III}, sequentially deprotection and *N*-*tert*-butoxycarbonyl (Boc) protection leads to intermediate **2** with 96% ee (84% yield). Compound **2** can be enantioenriched to >99.5% ee through a single recrystallization. Hydrogenolysis of

the azide and subsequent treatment with 3,5-bis-trifluoromethylphenyl isothiocyanate leads to the formation of a general structure of pyrrolidine thiourea catalysts. Finally, with the silylation and subsequent pyrrolidine deprotection catalysts **6a** and **6b** were obtained in good yields (Scheme 3.7).

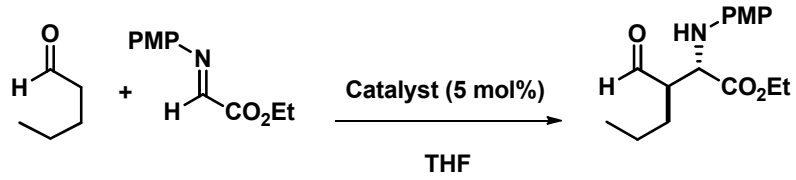


Scheme 3.7. Synthesis of catalysts **6a** and **6b**. a) i) $TMSN_3$ (*R*,*R*)-(salen)Cr^{III}, Et_2O, ii) K_2CO_3, iii) Boc_2O, Na_2CO_3, 84% (96% ee) or 67% recryst. (99.5% ee) b) H_2, PtO_2, MeOH, 93% c) 3,5-bis-trifluoromethylphenyl isothiocyanate, THF, 96% d) TBDMSCl or TBDPSCl, imidazole, DMF, 75-80% e) CF_3CO_2H, CH_2Cl_2, 92%.

Optimization and Screening

To test the efficiency of the catalysts, we decided to try the reaction of *N*-*p*-methoxyphenyl protected α-iminoglyoxylate with valeraldehyde as the model reaction. When the reaction was catalyzed by **6a,** good yields and moderate enantio- and diastereoselectivities were obtained. Also, benzoic acid was tested as an additive at different temperatures. However, best results were obtained at –40 ºC without any additive (Table 3.1, entry 3). With the catalyst **6b**, products were obtained with moderate yields, enantio- and diastereoselectivities; lowering the temperature or using additives did not improve the results. Compared to **6a**, catalyst **6b** showed slightly lower diastereoselectivity, which might be due to the smaller methyl- groups on the catalyst.

Table 3.1. Screening of the conditions for the catalytic asymmetric anti-Mannich-type reactions of an α-imino ester with valeraldehyde.

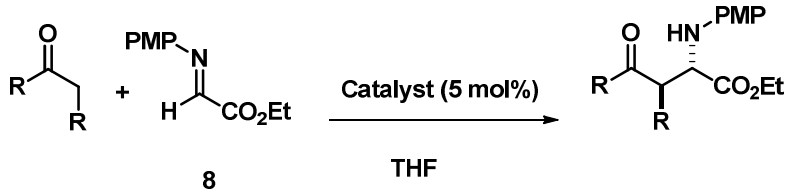


7 8 9

Entry	Catalyst	Additive	T(°C)	Yield%	ee%	dr
1	**6a**	-	–20	72	78	87:13
2	**6a**	PhCOOH	–20	67	71	82:18
3	**6a**	-	–40	85	81	87:13
4	**6a**	PhCOOH	–40	72	73	87:13
5	**6a**	-	–78	73	63	82:18
6	**6b**	-	–20	72	83	84:16
7	**6b**	PhCOOH	–20	77	81	73:27
8	**6b**	-	–40	56	73	80:20
9	**6b**	PhCOOH	–40	68	79	76:24
10	**6b**		–78	67	62	76:24

We screened some unmodified aldehydes at –20 ºC and ketones at 0 ºC. Although we have found that the best results are achieved at –40 ºC, the screening reactions were performed at higher temperatures due to the prolonged reaction times at lower temperatures. The aldehydes screened gave more or less moderate yields and selectivities except for isobutyraldehyde and cyclohexanecarboxaldehyde. In the case of isobutyraldehyde, after 30 h no product formation and for cyclohexanecarboxaldehyde no selectivity was observed with any of the two catalysts (Table 3.2). In the screening of ketones, longer reaction times were required for the conversion; however, selectivities of the formed products were lower than for the products obtained from aldehydes. When we compare our results with similar studies, we can conclude that, the shift of the face-shielding bulky group from position 2 in the pyrrolidine ring (by Peng)[25f] to position 4 (this work) has a negative effect on the diastereo- and enantioselectivity exhibited by **6a-b**.

Table 3.2. Scope of the *anti*-Mannich-type reaction of the unmodified aldehydes and ketones.



8

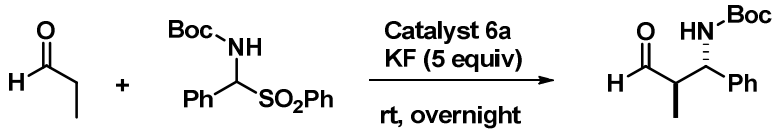
Carbonyl compound	T (ºC)	Time	Yield 6a	Yield 6b	dr % 6a	dr % 6b	ee % 6a	ee % 6b
Isobutyraldehyde	–20	30 h	-	-	-	-	-	-
Isovaleraldehyde	–20	5 h	70	61	86:14	85:15	67	79
Valeraldehyde	–20	3 h	72	72	87:13	84:16	78	83
Heptanal	–20	2 h	86	60	88:12	81:19	89	86
Hydrocinnamaldehyde	–20	15 h	56	60	79:21	73:27	73	83
Cyclohexane carboxaldehyde	0	2 d	63	50	-	-	0	10
9-Decenal	–20	45 min	80	75	85:15	85:15	79	82
2-Butanone	0	3d	28	23	-	-	-	-
Cyclohexanone	0	24 h	52	49	66:34	78:22	55	67
1,4-Cyclohexanedione mono-ethylene acetal	0	2 d	66	71	83:17	88:12	55	67
Tetrahydro-4H-pyran-4-one	0	24 h	67	62	82:18	85:15	53	57

After screening of aldehydes and ketones we turned our attention towards a different imine, which was prepared *in situ* from α-amido sulfones and inorganic bases. These types of *in situ* generated carbamate-protected imines were used in Mannich reactions primarily by Melchiorre and co-workers.[27] Thus, we tested our catalysts in the reaction of *in situ* formed *N*-Boc imino ester with propanal. Although good yields were obtained, the selectivity of the catalysts remained lower

[27] a) Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47,* 8700-8702. b) Galzerano, P.; Agostino, D.; Bencivenni, G.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2010**, *16*, 6069-6076.

with 10 or 20 mol% catalyst loadings and changing the solvent did not improve this selectivity.

Table 3.3. *Anti*-Mannich reaction of propanal with in situ generated *N*-Boc imine.



9 **10** **11**

Catalyst	Solvent	Yield%	ee%	dr
10 mol%	DCM	95	42	1.3:1
10 mol%	Toluene	87	53	1.2:1
10 mol%	THF	82	64	1.25:1
10 mol%	AcN	97	55	1.3:1
20 mol% [a]	THF	74	50	1.2:1
20 mol% [b]	THF	70	54	1.2:1

[a] Reaction at 30 °C, 4 d

[b] Reaction with catalyst **6b**

After this point, even though we continued further utilizing these catalysts under different conditions and in some other reactions, we were unable to improve the results in terms of enantio- and diastereoselectivities. For this reason, we decided to change the design of our catalyst for the following studies.

3.5. CONCLUSION

In this study, the catalysts prepared via desymmetrization of *meso*-*N*-trifluoroacetyl-3-pyrroline oxide allowed us for the functionalization of pyrrolidine ring from C3 and C4 positions. In comparison, a similar study published by Peng *et al.,* in which active and selective *anti*-Mannich catalysts have a thiourea motif in C4 position and a bulky face shielding group in C2 position. Even though we can obtain different catalysts with this desymmetrization step, the positions for the functionalization of the catalyst backbone may not be in the proper array for a selective reaction. Further modification of this catalyst might allow for the synthesis

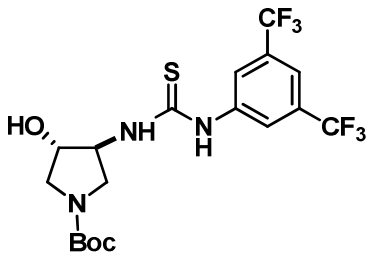
of more active and selective pyrrolidine-based thiourea organocatalysts for the enantioselective *anti*-Mannich reaction.

3.6. EXPERIMENTAL SECTION

General Methods and Materials

Unless otherwise stated, all reactions were carried out under N_2. Synthesis grade solvents were used as received. Aldehydes were distilled prior to use and ketones were used as received. All flash chromatographies were carried out using 60 mesh silica gel and dry-packed columns. The ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^1H or at 100 MHz and 125 MHz for ^{13}C, respectively. ^1H NMR spectroscopy chemical shifts are quoted in ppm relative to internal tetramethylsilane (TMS) and ^{13}C NMR spectra to $CDCl_3$. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier Instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Specific optical rotation measurements were carried out on a Jasco P-1030 model polarimeter equipped with a PMT detector using the Sodium line at 589 nm. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralcel AS-H and IC guard columns as noted. PMP-protected α-iminoester **8**[25b,c] and N-Boc imino ester **10**[28] were synthesized following reported procedures. In the synthesis of catalysts, intermediates **2** and **3** were prepared according to reported procedures.[19]

Synthesis of Ligands



(3*S*,4*S*)-*tert*-butyl 3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-hydroxy-pyrrolidine-1-carboxylate (4)

[28] Dong, D. J.; Li, H. H.; Tian, S. K. *J. Am. Chem. Soc*. **2010**, *132*, 5018-5020.

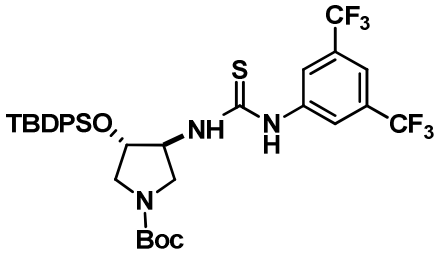
To a solution of amino alcohol **3** (1.98 mmol, 0.400 g) in anhydrous THF (15 mL) was added 3,5-bis(trifluoromethyl) phenyl isothiocyanate (1.05 equiv, 2.08 mmol, 0.38 mL) at room temperature. The solution was stirred overnight until TLC analysis indicated the completion of the reaction. Then, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography with CH_2Cl_2/MeOH (100:0 to 95:5) eluent system. The desired product was obtained as a light yellow foam in 96% yield.

^{1}H NMR (400 MHz, CH_3OD): δ 8.21 (s, 2H), 7.62 (s, 1H), 4.67 (br s, 1H), 4.36 (br s, 1H), 3.81 (dd, *J* = 5.1, 11.1 Hz, 1H), 3.60-3.55 (m, 1H), 3.39 (dd, *J* = 2.4, 11.7 Hz, 1H), 3.34 (dd, *J* = 1.9, 11.9 Hz, 1H), 1.48 (s, 9H).

^{13}C NMR (100 MHz, CH_3OD): δ 181.7, 155.1, 141.7, 131.3 (q, *J* = 33.4 Hz), 123.4 (q, *J* = 271.8 Hz), 122.3, 116.6, 79.9, (73.1-72.4*), (60.0-59.2*), (51.7-51.2*), (49.0-48.4*), 27.3.

*The peaks in parenthesis indicate the rotamers.

HRMS (ESI+): *m/z* = 496.1106, calcd. for $C_{18}H_{21}N_3O_3SF_6Na$ $[M+Na]^+$, found 496.1115.



(3*S*,4*S*)-*tert*-butyl 3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-((*tert*-butyl-diphenylsilyl)oxy)pyrrolidine-1-carboxylate (5a)

A 25-mL round-bottom flask was charged with (3*S*,4*S*)-*tert*-butyl 3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-hydroxypyrrolidine-1-carboxylate (**4**) (1.00 mmol, 0.47 g) in *N*,*N*-dimethylformamide (10 mL) to give a colorless solution. Then, imidazole (8.00 mmol, 0.54 g) and TBDPSCl (4.00 mmol, 1.09 g) were added sequentially. The colorless reaction solution was allowed to stir overnight at room temperature. After the TLC analysis indicated the completion of the reaction, the mixture was poured onto saturated NH_4Cl solution (75mL) and extracted with ethyl acetate (3 x 20mL). The organic layers were combined and treated with brine (20 mL). Then, the organic phase was dried over anhydrous $MgSO_4$ and filtered.

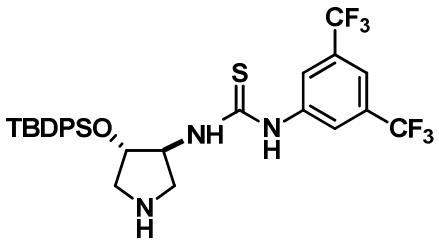
Volatiles were removed under reduced pressure and the product was purified by flash column chromatography using hexanes to hexane/ethyl acetate (90:10) as eluent. The product was obtained as a white foam in 79% yield.

^{1}H NMR (400 MHz, CH_3OD): δ 8.18 (s, 2H), 7.75-7.67 (m, 4H), 7.63 (s, 1H), 7.46-7.39 (m, 6H), 4.93 (br s, 1H), 4.46 (d, *J* = 19.2 Hz, 1H), 3.93 (dd, *J* = 5.7, 11.6 Hz, 1H), 3.44 (dd, *J* = 5.4, 11.4 Hz, 1H), 3.34-3.32 (m, 1H), 3.24-3.19 (m, 1H), 1.51 (s, 4H), 1.44 (s, 5H), 1.09 (s, 9H).

^{13}C NMR (100 MHz, CH_3OD): δ 181.6, 155.2, 141.7, 135.7, 135.5, 133.5, 133.3, 132.7, 131.3 (q, *J* = 33.3 Hz), 129.8, 127.6, 127.5, 123.4 (q, *J* = 271.8 Hz), 122.3, 116.6, (80.1-79.9*), (75.3-74.7*), (60.3-59.7*), (52.0-51.8*), (49.4-48.9*), 27.4, 26.0, 18.6.

*The peaks in parenthesis indicate the rotamers.

HRMS (ESI+): *m/z* = 734.2283, calcd. for $C_{34}H_{39}N_3O_3F_6SSiNa$ $[M+Na]^+$, found 734.2274.



1-(3,5-bis(trifluoromethyl)phenyl)-3-((3*S*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-pyrrolidin-3-yl)thiourea (6a)

A 10 mL round-bottom flask was charged with (3*S*,4*S*)-*tert*-butyl 3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1-carboxylate (**5a**) (0,70 mmol, 0.50 g) and dissolved in CH_2Cl_2 (5 mL). The temperature was lowered to 0 ºC in an ice bath, trifluoroacetic acid (1.35 mL) was added and the mixture was allowed to reach rt. Reaction was completed in 3 h and after that an aqueous solution of sodium carbonate (10 mL, 10% w/w) was added dropwise to the reaction mixture (exothermic reaction!). Phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 4 mL). The combined organic phases were, dried over Na_2SO_4 and filtered. Volatiles were removed under reduced pressure. The product was isolated with flash column

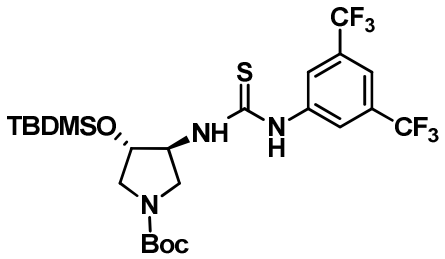
chromatography CH_2Cl_2/MeOH (100 to 95:5) solvent system was used as an eluent. The product was obtained as a light yellow foam with 93% yield.

^{1}H NMR (400 MHz, CH_3OD): δ 8.10 (s, 2H), 7.73-7.67 (m, 4H), 7.61 (s, 1H), 7.42-7.36 (m, 5H), 4.93 (br s, 1H), 4.42-4.39 (m, 1H), 3.60 (dd, *J* = 6.58, 12.2 Hz, 1H), 3.06 (dd, *J* = 4.9, 12.4 Hz, 1H), 3.01-2.97 (m, 2H), 1.08 (s, 9H).

^{13}C NMR (100 MHz, CH_3OD): δ 181.5, 141.6, 135.7, 135.6, 132.9, 132.7, 131.3 (q, *J* = 33.3 Hz), 129.9, 129.8, 127.7, 127.6, 123.4 (q, *J* = 271.8 Hz), 122.6, 116.7, 77.3, 67.5, 62.1, 52.7, 50.0, 25.1, 18.5.

HRMS (ESI+): *m/z* = 612.1940, calcd. for $C_{29}H_{32}N_3OF_6SiS$ $[M+H]^+$, found 612.1963.

$[\alpha]_D^{25}$ = –8.49 (c = 0.96 in $CHCl_3$).



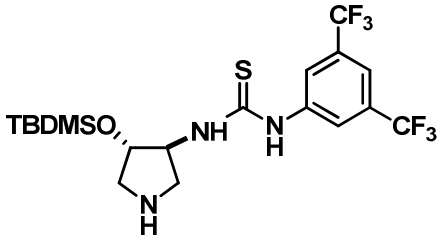
(3*S*,4*S*)-*tert*-butyl 3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-((*tert*-butyl-dimethylsilyl)oxy)pyrrolidine-1-carboxylate (5b)

A 25-mL round-bottom flask was charged with (3*S*,4*S*)-*tert*-butyl 3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-hydroxypyrrolidine-1-carboxylate (**4**) (0.8 mmol, 0.38 g) in *N*,*N*-dimethylformamide (10 mL) to give a colorless solution. Then, imidazole (1.6 mmol, 0.11 g) and TBDPSCl (3.2 mmol, 0.48 g) were added sequentially. The colorless solution was allowed to stir overnight at room temperature. After the TLC analysis indicated the completion of the reaction, the mixture was poured onto saturated NH_4Cl solution (75 mL) and extracted with ethyl acetate (3 x 20 mL). The organic layers were combined and treated with brine (20 mL). Then organic phase dried over anhydrous $MgSO_4$, and filtered. Volatiles were removed under reduced pressure and the product was purified by short flash column chromatography using hexanes to hexanes/ethyl acetate (90:10) as eluent. The desired product obtained was obtained as a white foam in 65% yield.

^{1}H NMR (400 MHz, CH_3OD): δ 8.23 (s, 2H), 7.65 (s, 1H), 4.65 (br s, 1H), 4.48 (d, *J* = 12.3 Hz, 1H), 3.77-3.74 (m, 1H), 3.56-3.51 (m, 1H), 3.42 (dd, *J* = 3.9, 11.5 Hz, 1H), 1.50 (s, 9H), 0.94 (s, 9H), 0.23 (s, 3H), 0.18 (s, 3H).

^{13}C NMR (100 MHz, CH_3OD): δ 181.7, 155.3, 141.7, 131.3 (q, J = 33.3 Hz), 123.4 (q, J = 271.8 Hz), 122.3, 116.6, 80.0, (74.4-73.7*), (60.3-59.6*), (52.7-52.1*), (48.9-48.3*), 27.3, 24.9, 17.4, –5.4, –6.0.

*The peaks in parenthesis indicate the rotamers.



1-(3,5-bis(trifluoromethyl)phenyl)-3-((3*S*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-pyrrolidin-3-yl)thiourea (6b)

A 10-mL round-bottom flask was charged with (3*S*,4*S*)-*tert*-butyl 3-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-4-((*tert*-butyldiphenylsilyl)oxy)pyrrolidine-1-carboxylate (**5a**) (0,27 mmol, 0.16 g) and dissolved in CH_2Cl_2 (2.5 mL). At 0 ºC, trifluoroacetic acid (0.6 mL) was added and the mixture was allowed to reach rt. Reaction was completed in 3 h and after that an aqueous solution of sodium carbonate (10 mL, 10% w/w) was added dropwise to the reaction mixture (exothermic reaction!). Phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 4 mL). The combined organic phases were dried over Na_2SO_4 and filtered. Volatiles were removed under reduced pressure and the product was isolated with flash column chromatography using CH_2Cl_2/MeOH (100 to 95:5) as an eluent. The product was obtained as a light yellow foam in 85% yield.

^{1}H NMR (400 MHz, CH_3OD): δ 8.19 (s, 2H), 7.60 (s, 1H), 4.61 (br s, 1H), 4.40-4.37 (m, 1H), 3.43 (dd, *J* = 6.3, 12.2 Hz, 1H), 3.08 (dd, *J* = 4.5, 12.1 Hz, 1H), 2.84 (dd, *J* = 2.8, 12.1 Hz, 1H), 0.9 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H).

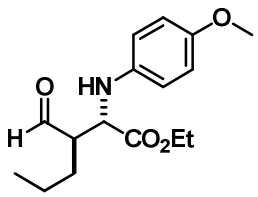
^{13}C NMR (100 MHz, CH_3OD): δ 181.6, 141.9, 131.3 (q, *J* = 33.3 Hz), 123.4 (q, *J* = 271.6 Hz), 122.4, 116.5, 77.0, 62.4, 53.1, 49.7, 24.9, 17.5, –5.6, –6.0.

HRMS (ESI+): *m/z* = 488.1627, calcd. for $C_{19}H_{28}N_3OSF_6Si$ $[M+H]^+$, found 488.1620.

$[\alpha]_D^{25}$ = –7.99 (c = 1.01 in $CHCl_3$).

General Reaction Conditions for *Anti*-Mannich Reactions

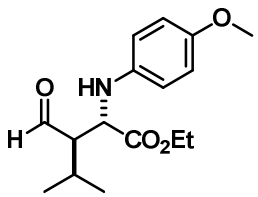
N-PMP-protected α-imino ethyl glyoxylate (41 mg, 0.2 mmol) was dissolved in anhydrous CH_2Cl_2 (1.5 ml) and then, the aldehyde (1 mmol, 140μL), and catalyst (5 mol%) (0.01 mmol, 6.1 mg) were sequentially added. Consumption of the imine was controlled by TLC and the mixture was stirred until the reaction was completed. At the end, the reaction mixture was worked up with the addition of aq. NH_4Cl solution (3 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine and dried over Na_2SO_4. Volatiles were removed under reduced pressure and the product was isolated by flash column chromatography using (5-10%) EtOAc/Hexanes as the eluent system.



(2*S*,3*R*)-ethyl 3-formyl-2-((4-methoxyphenyl)amino)hexanoate (9)[25f]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 85% yield and 81% ee.

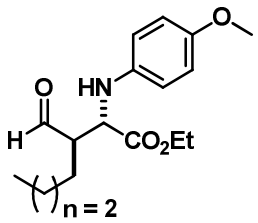
HPLC: AS-H column, hexane/*i*-PrOH (98:2), 0.5 mL·min^{-1}, 254 nm, t_R major = 50.7 min, t_R minor = 67.0 min.



(2*S*,3*R*)-ethyl 3-formyl-2-((4-methoxyphenyl)amino)-4-methylpentanoate[25f]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 61% yield and 67% ee.

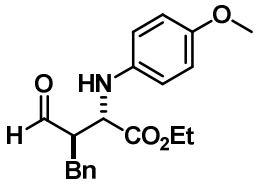
HPLC: AS-H column, hexane/*i*-PrOH (90:10), 0.5 mL·min^{-1}, 254 nm, t_R major = 17.8 min, t_R minor = 35.2 min.



(2*S*,3*R*)-ethyl 3-formyl-2-((4-methoxyphenyl)amino)octanoate[25f]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 86% yield and 89% ee.

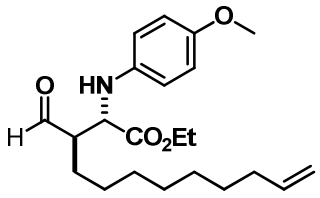
HPLC: AS-H column, hexane/*i*-PrOH (98:2), 0.5 mL·min^{-1}, 254 nm, t_R major = 44.1 min, t_R minor = 51.6 min.



(2*S*,3*R*)-ethyl 3-benzyl-2-((4-methoxyphenyl)amino)-4-oxobutanoate[19]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 56% yield and 73% ee.

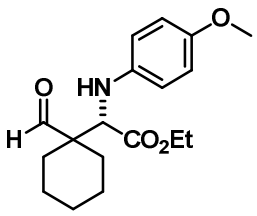
HPLC: AS-H column, hexane/*i*-PrOH (98:2), 1.0 mL·min^{-1}, 240 nm, t_R major = 53.0 min, t_R minor = 59.3 min.



(2S,3R)-ethyl 3-formyl-2-((4-methoxyphenyl)amino)dodec-11-enoate[19]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 80% yield and 79% ee.

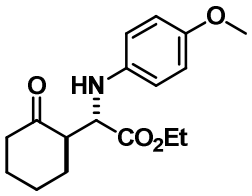
HPLC: IC column, hexane/*i*-PrOH (90:10), 1.0 mL·min^{-1}, 240 nm, t_R minor = 11.7 min, t_R major = 12.3 min.



(*S*)-ethyl 2-(1-formylcyclohexyl)-2-((4-methoxyphenyl)amino)acetate[25f]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 50% yield and 10% ee.

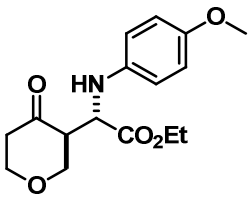
HPLC: AS-H column, hexane/*i*-PrOH (90:10), 0.5 mL·min^{-1}, 254 nm, t_R major = 13.7 min, t_R minor = 14.8 min.



(*S*)-ethyl 2-((4-methoxyphenyl)amino)-2-((*R*)-2-oxocyclohexyl)acetate[25f]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 52% yield and 55% ee.

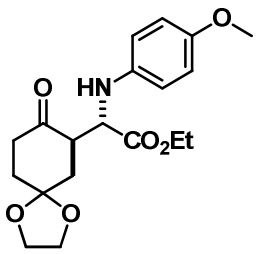
HPLC: AS-H column, hexane/*i*-PrOH (90:10), 0.5 mL·min^{-1}, 254 nm, t_R major = 27.7 min, t_R minor = 38.1 min.



(*S*)-ethyl 2-((4-methoxyphenyl)amino)-2-((*S*)-4-oxotetrahydro-2H-pyran-3-yl)acetate[19]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 67% yield and 53% ee.

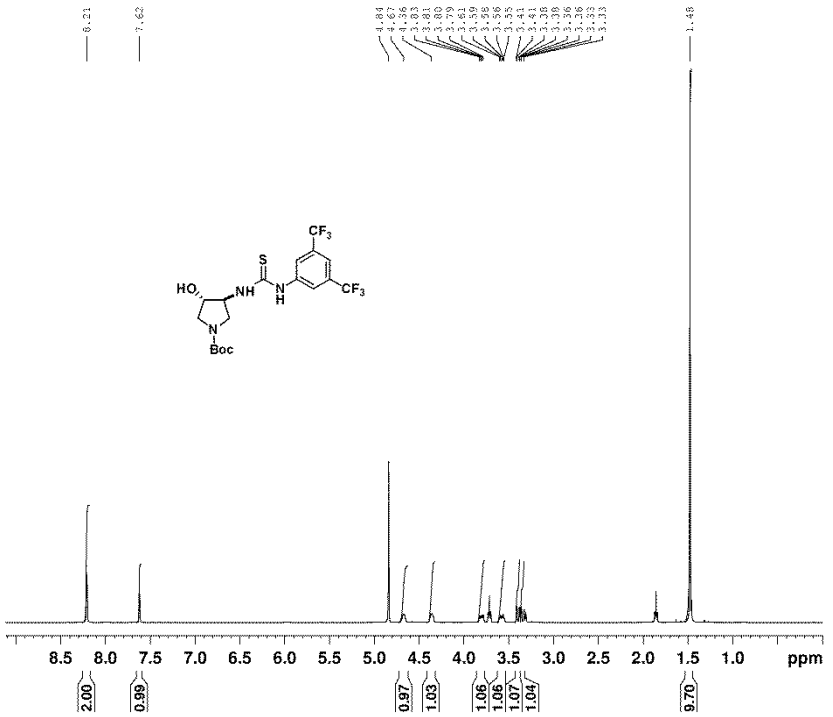
HPLC: IC column, hexane/*i*-PrOH (90:10), 0.5 mL·min^{-1}, 240 nm, t_R minor = 31.6 min, t_R major = 35.1 min.



Ethyl(2S, 1′R)-2-(p-methoxyphenylamino)-2-(5′, 5′-ethylenedioxy-2′-oxocyclo-hexyl)acetate[25f]

Following the general procedure for *anti*-Mannich reaction as described above the title compound was obtained in 71% yield and 55% ee.

HPLC: IC column, hexane/*i*-PrOH (85:15), 1.0 mL·min^{-1}, 240 nm, t_R minor = 23.1 min, t_R major = 28.4 min.

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DE                6.00 usec
TE                298.0 K
D1             1.00000000 sec
TD0                    1

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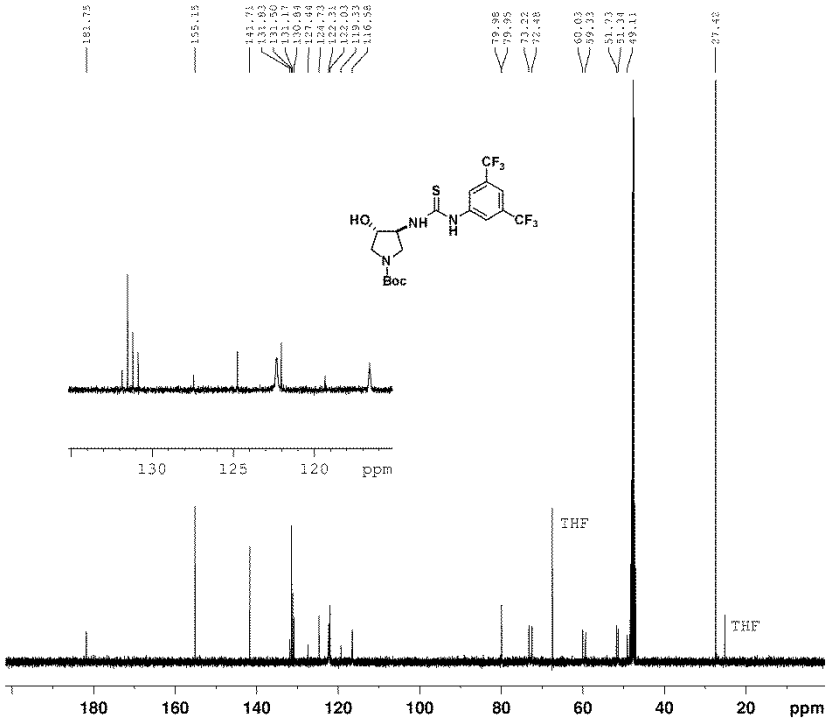


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SOLVENT             MeOD
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RG                 20642.5
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DE                6.00 usec
TE                298.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                    1

========== CHANNEL f1 ==========
NUC1                  13C
P1                 7.00 usec
PL1               -5.00 dB
PL1W         119.14923859 W
SFO1          100.6228298 MHz

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NUC2                  1H
PCPD2              80.00 usec
PL2               -4.00 dB
PL12              13.89 dB
PL13              13.89 dB
PL2W          37.85744095 W
PL12W         0.61539114 W
PL13W         0.61539114 W
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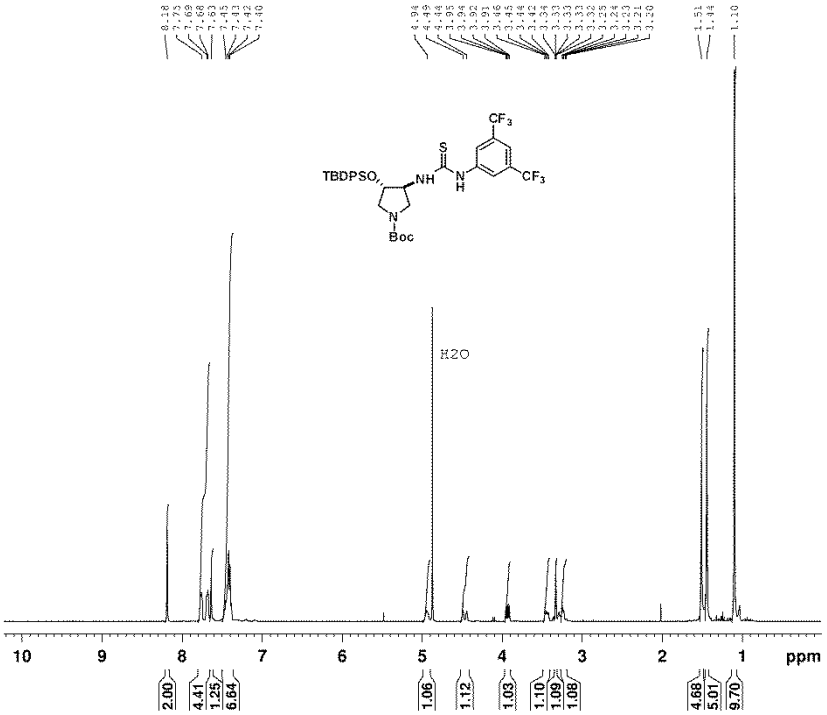

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SOLVENT	MeOD
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DE	6.00 usec
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PL1W	37.85744095 W
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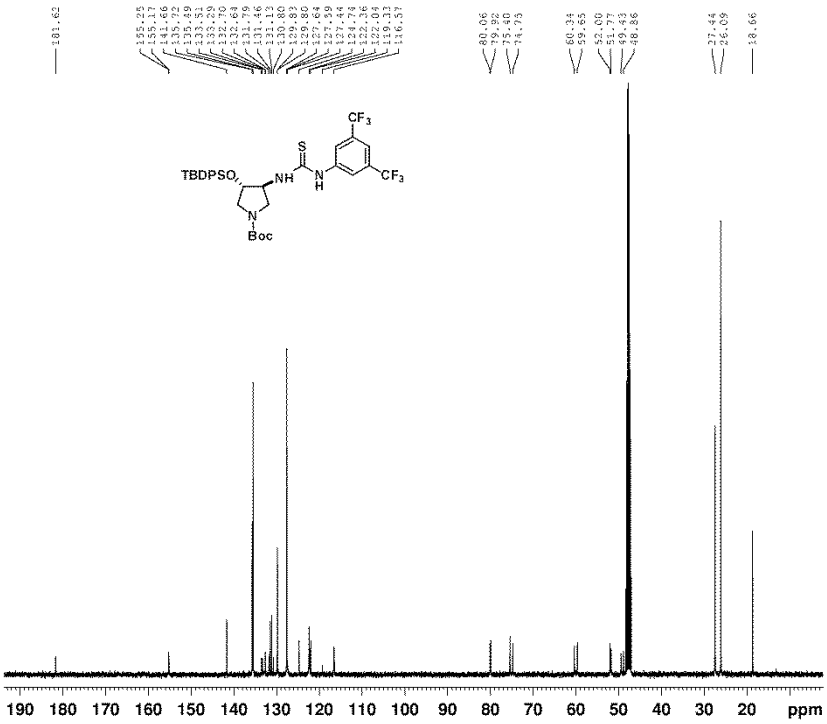

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SOLVENT	MeOD
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AQ	1.3664756 sec
RG	26008
DW	20.850 usec
DE	6.00 usec
TE	298.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	7.00 usec
PL1	-5.00 dB
PL1W	119.14923859 W
SFO1	100.6228298 MHz
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NUC2	1H
PCPD2	80.00 usec
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PL12	13.89 dB
PL13	13.89 dB
PL2W	37.85744095 W
PL12W	0.61539114 W
PL13W	0.61539114 W
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WDW	EM
SSB	0
LB	1.00 Hz
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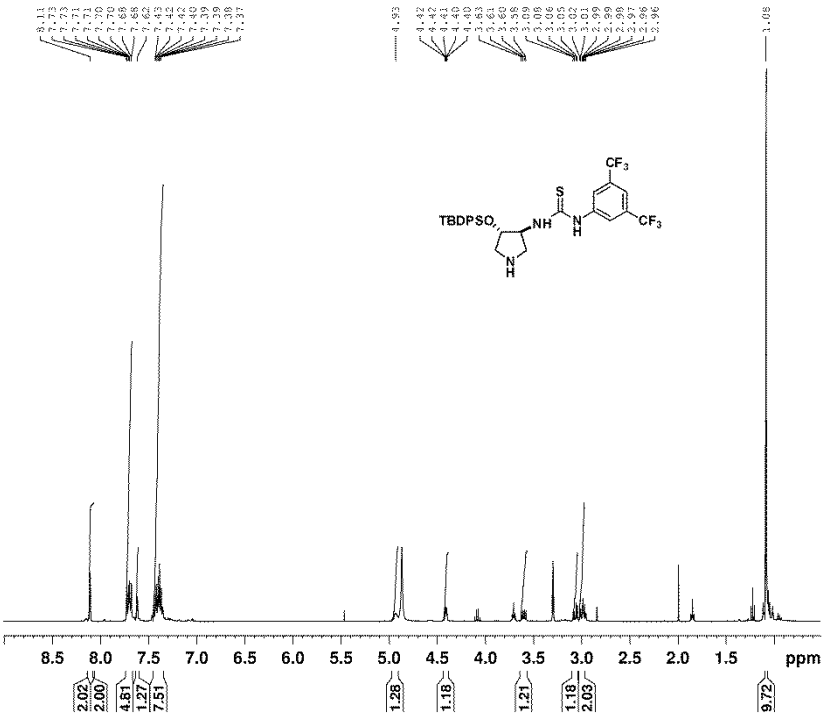
PC	1.40



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TE	298.0 K
D1	1.00000000 sec
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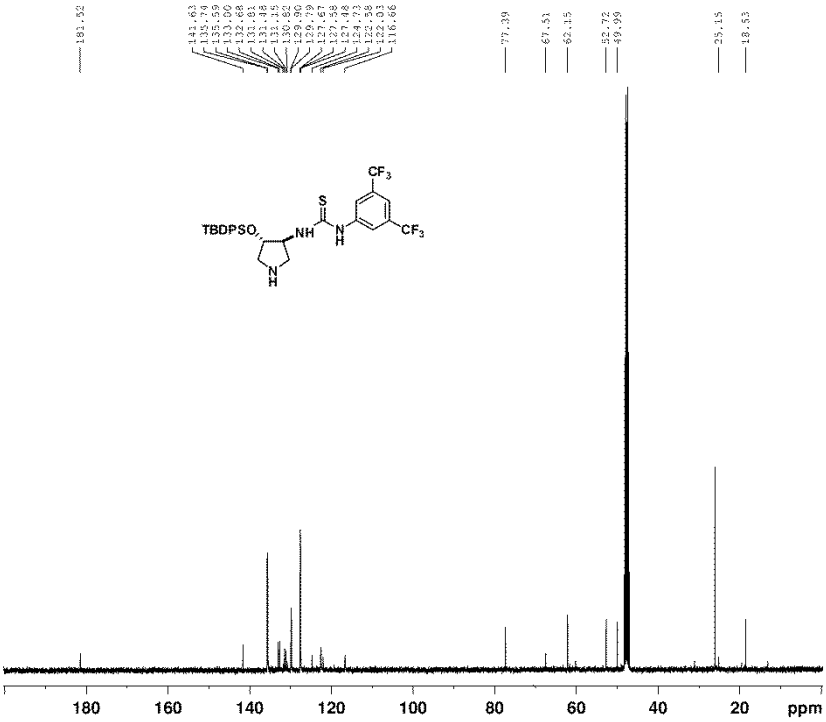

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SOLVENT	MeOD
NS	512
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FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	13004
DW	20.850 usec
DE	6.00 usec
TE	298.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
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PL1	-5.00 dB
PL1W	119.14923859 W
SFO1	100.6228298 MHz
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NUC2	1H
PCPD2	80.00 usec
PL2	-4.00 dB
PL12	13.89 dB
PL13	13.89 dB
PL2W	37.85744095 W
PL12W	0.61539114 W
PL13W	0.61539114 W
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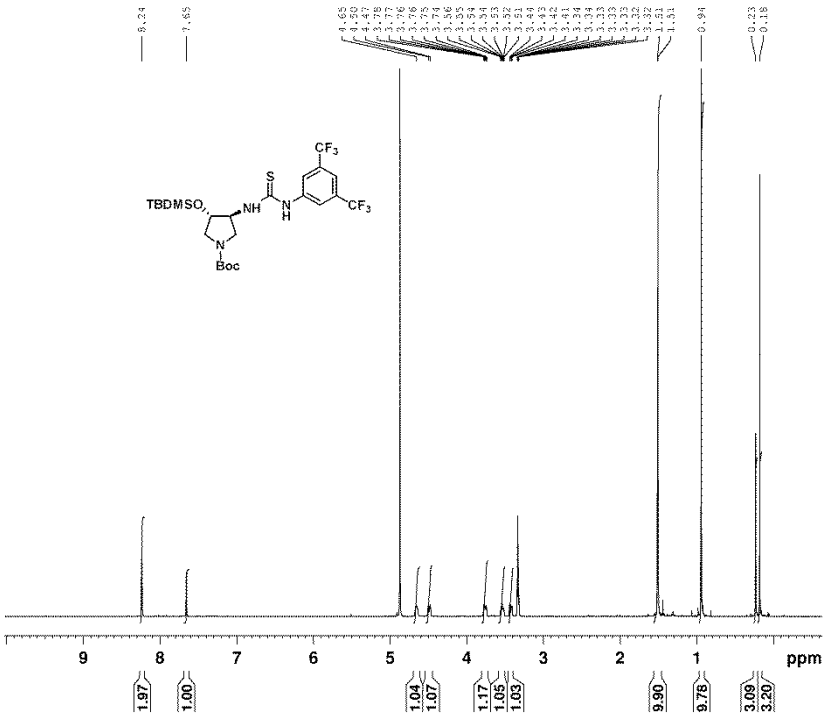


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PROCNO                   1
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TD                 32768
SOLVENT             MeOD
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DW              83.200 usec
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TE                298.0 K
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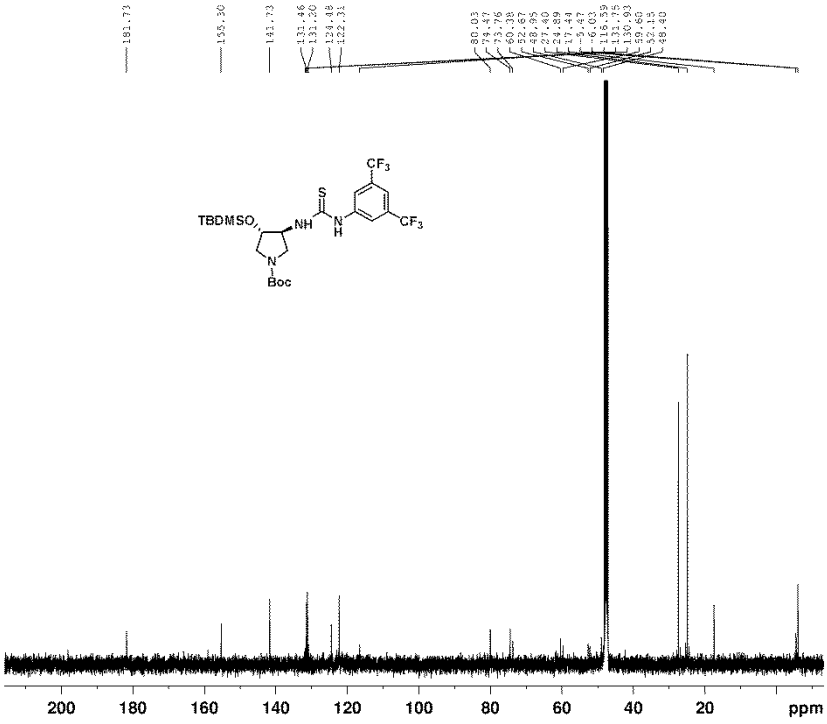


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PROCNO                   1
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TD                 65536
SOLVENT             MeOD
NS                  1024
DS                     4
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FIDRES        0.462388 Hz
AQ            1.0814105 sec
RG                   812
DW              16.500 usec
DE              10.00 usec
TE                298.0 K
D1            3.00000000 sec
D11           0.03000000 sec
TD0                    1

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PL1                0.00 dB
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SFO1        125.7703648 MHz

======== CHANNEL f2 ========
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PCPD2            80.00 usec
PL2                3.00 dB
PL12              18.14 dB
PL13              18.14 dB
PL2W        12.58925438 W
PL12W       0.38547841 W
PL13W       0.38547841 W
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SI                 32768
SF          125.7577890 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                1.40
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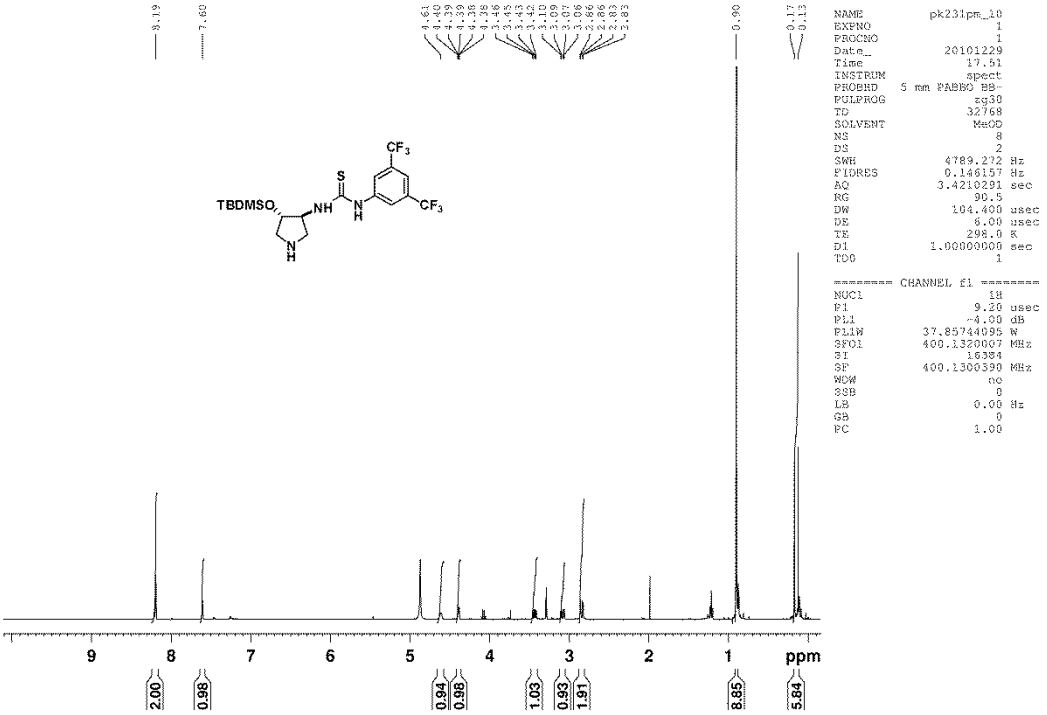


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DS                        2
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RG                      90.5
DW                   104.400 usec
DE                      6.00 usec
TE                    298.0 K
D1                 1.00000000 sec
TD0                       1

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PL1                   -4.00 dB
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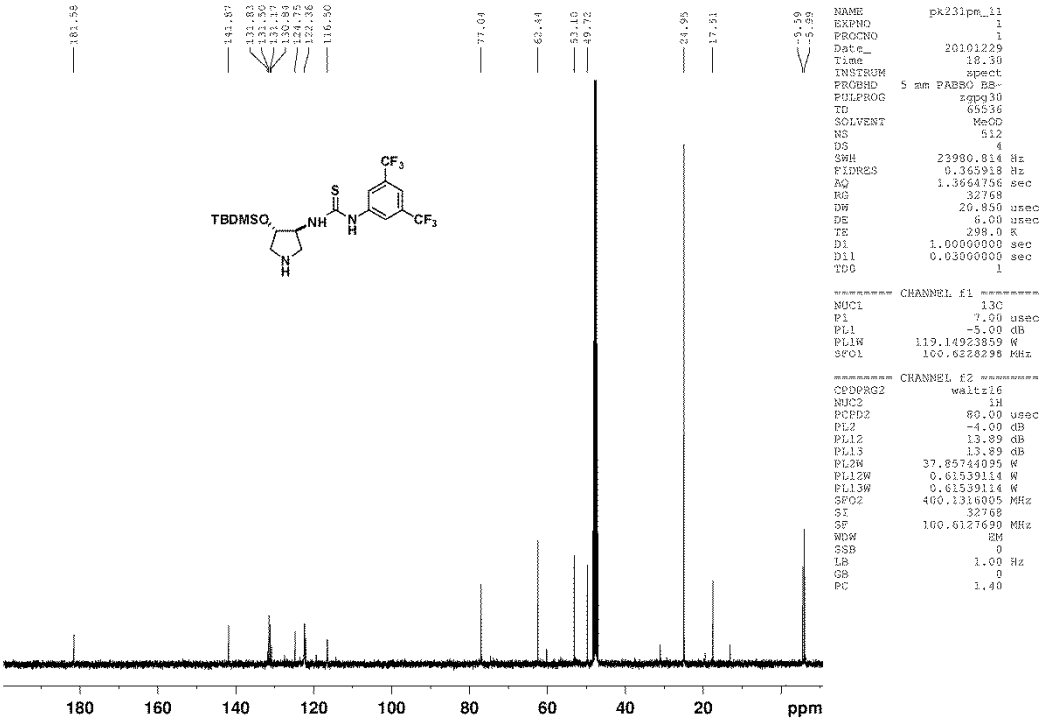


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SOLVENT                MeOD
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DS                        4
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RG                    32768
DW                   20.850 usec
DE                      6.00 usec
TE                    298.0 K
D1                 1.00000000 sec
D11                0.03000000 sec
TD0                       1

========== CHANNEL f1 ==========
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P1                     7.00 usec
PL1                   -5.00 dB
PL1W           119.14923859 W
SFO1           100.6228298 MHz

========== CHANNEL f2 ==========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -4.00 dB
PL12                  13.89 dB
PL13                  13.89 dB
PL2W           37.85744095 W
PL12W           0.61539114 W
PL13W           0.61539114 W
SFO2           400.1316005 MHz
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SF             100.6127690 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
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CHAPTER IV

4. POLYSTYRENE-SUPPORTED HYDROGEN BONDING ORGANOCATALYSTS

4-I. POLYSTYRENE-SUPPORTED SQUARAMIDE ORGANOCATALYSTS FOR ENANTIOSELECTIVE MICHAEL ADDITION REACTIONS

4.1. SQUARAMIDES

Squaramides, which are amides derived from squaric acid, feature a rigid four membered ring system in their structure and are remarkable compounds due to their high hydrogen bond acceptor and donor ability. These outstanding cyclic structures allow the formation of up to four hydrogen bonds through binding of both anions and cations.[1] Due to these interesting features squaramides have been used in different areas like biochemistry, medicinal chemistry, supramolecular chemistry and as asymmetric catalysts in synthetic chemistry. Their dual character allows them to interact with both cations and anions, which makes them important for biological investigations. Similar to life-essential processes in human body, most of the biological processes in the human body occur via molecular recognition (Figure 4.1).[2]

The studies on the physical properties of squaramides have shown that, when they are used for cation recognition (for instance ammonium cations), a complex **4.1b** formed via H-bonding by the help of H-bond acceptor groups. The measured aromaticity of the newly formed ammonium cation complex **4.1b** was found to be higher than that of squaramide itself (**4.1a**).[1a,c,d] It has also been found that an increase in aromaticity by binding also increases the H-bond acceptor property of squaramides. Similar researches have been done on squaramides for

[1] a) Tomàs, S.; Prohens, R.; Vega, M.; Rotger, M. C.; Deyà, P. M.; Ballester, P.; Costa, A. *J. Org. Chem.* **1996**, *61*, 9394-9401. b) Prohens, R.; Tomàs, S.; Morey, J.; Deyà, P. M.; Ballester, P.; Costa, A. *Tetrahedron Lett.* **1998**, *39*, 1063-1066. c) Quiñonero, D.; Frontera, A.; Ballester, P.; M. Deyà, *Tetrahedron Lett*. **2000**, *41*, 2001-2005. d) Quiñonero, D.; Prohens, R.; Garau, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà, P. M. *Chem. Phys. Lett*. **2002**, *351*, 115-120. e) Garau, C.; Frontera, A.; Ballester, P.; Quiñonero, D.; Costa, A.; Deyà, P. M. *Eur. J. Org. Chem*. **2005**, *1*, 179-183. f) Rotger, C.; Soberats, B.; Quiñonero, D.; Frontera, A.; Ballester, P.; Benet-Buchholtz, J.; Deyà, P. M. *Eur. J. Org. Chem*. **2008**, 11, 1864-1868.

[2] a) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. *Chem. Eur. J.* **2011**, *17*, 6890-6899. b) Storer, I. R.; Aciro, C.; Jones, L. H. *Chem. Soc. Rev*. **2011**, *40*, 2330-2346.

anion recognition.[1b,d,e] The results have shown that, as in the case of cation binding, the aromaticity of the complex **4.1b** was increased in anion binding.

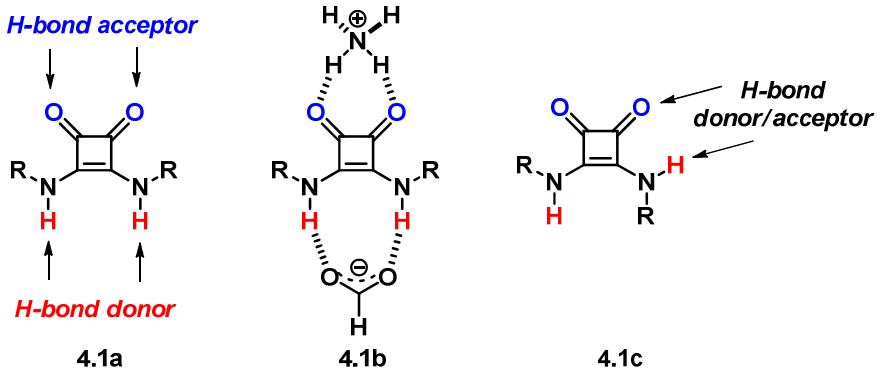


Figure 4.1. Representation of dual character and H-bonding structures in squaramides.

One of the other special features of squaramides apart from aromaticity is their rigid and planar structure provided by the two coplanar carbonyl and the two NH groups. Conjugation is possible from N(p-orbital) to the π system of the plane (Figure 4.2 (A)) so that the planar conformation is stabilized by nitrogen lone pair conjugation. This lone pair delocalization consequently restricts the rotation of the C–N bond.[2b] [3] Thus, there are two different conformations for the NH groups: *anti/anti* and *syn/anti*; the preferred conformation is *anti/anti* due to the rotation restrictions from C–N bonds.[1d,4]

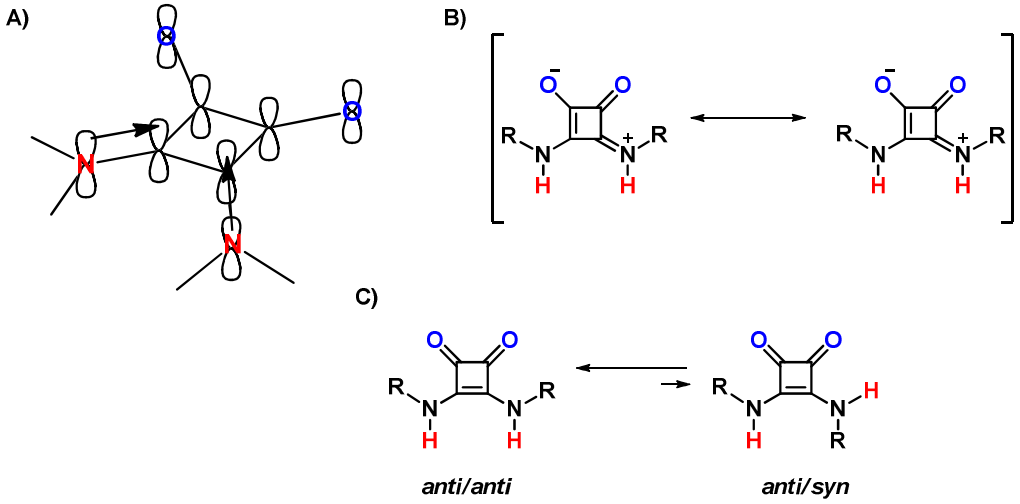


Figure 4.2. A) Lone pair conjugation, B) resonance forms and C) conformations of squaramides.

[3] Rotger, M. C.; Pina, M. N.; Frontera, A.; Martorell, G.; Ballester, P.; Deyà, P. M.; Costa, A. *J. Org. Chem.* **2004**, *69*, 2302-2308.
[4] Muthyala, R. S.; Subramaniam. G.; Todaro, L. *Org. Lett.* **2004**, *6*, 4663-4665. b) Fu, N.; Allen, A. D.; Kobayashi, S.; Tidwell, T. T.; Vukovic, S.; Arumugam, S.; Popik, V. V.; Mishima, M. *J. Org. Chem.* **2007**, *72*, 1951-1956. c) Ramalingam, V.; Domaradzki, M. E.; Jang, S.; Muthyala, R. S. *Org. Lett.* **2008**, *10*, 3315-3318.

Squaramides are an important class of H-bonding structures, but polyammoniums/guanidiniums, calixarenes, amides, ureas or thioureas are other structures used for similar applications.[5] Among various H-bonding structures, ureas and thioureas are closer structures to the squaramides. However squaramides differ from them distinctively in terms of duality in character, rigidity (aromaticity), H-bond spacing between two NH groups, H-bond angle and acidity.[2a]

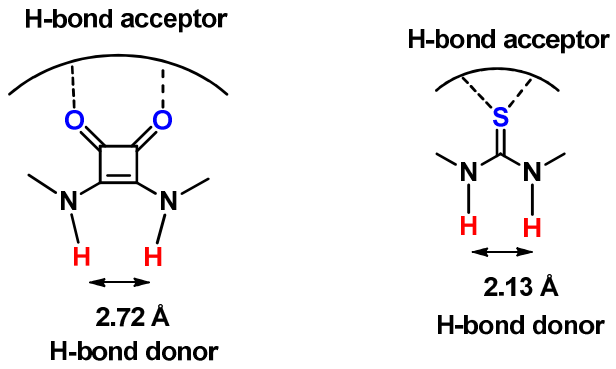


Figure 4.3. Comparison of the H-bond spacing between *N*,*N*-dimethylthiourea and *N*,*N*-dimethylsquaramide.

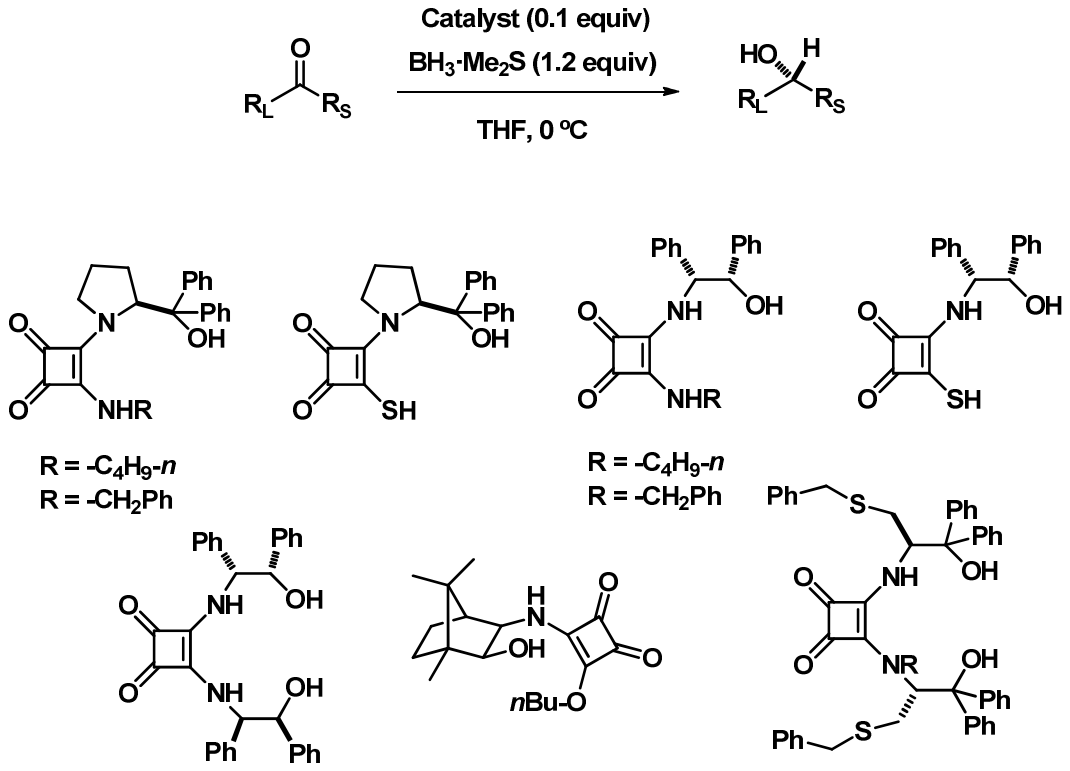
According to studies carried out by Takemoto *et al.,* the calculated distance of NH protons in *N*,*N*-dimethylthiourea is approximately 2.13 Å. The same calculation has been done for *N*,*N*-dimethylsquaramide by the Rawal group and the distance calculated was 2.72 Å (Figure 4.3).[6] The H-bond angle in squaramides has been found to be convergent and this property is thought to be resulting from the cyclobutenedione ring square geometric structure.[6b] Furthermore, the two carbonyls in squaramide are able to form strong acceptor interactions compared to the single carbonyl in ureas. Overall, these differences between squaramides and (thio)ureas may offer better or complementary reactivity.

[5] a) Scheerder, J.; Engbersen, J. F. J.; Casnati, A.; Ungaro, R.; Reinhoudt, D. N. *J. Org. Chem.* **1995**, *60*, 6448-6454. b) Beer, P. B. *J. Chem. Soc. Chem. Commun*. **1996**, *6*, 689-696. c) Takemoto, Y. *Org. Biomol. Chem*. **2005**, *3*, 4299-4306. d) Coles, M. P. *Chem. Commun*. **2009**, *25* 3659-3676.
[6] a) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc*. **2005**, *127*, 119-125. b) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc*. **2008**, *130*, 14416-14417.

4.1.1. Applications of Squaramides in Synthesis

4.1.1.1. Squaramides as Chiral Ligands

The squaramide motif was first used in asymmetric catalysis by Zhou *et al.* in 2001.[7] They synthesized different chiral squaric acid amino alcohols and C_2-symmetric diamino alcohols, and then they formed in situ chiral boron heterocycles with them. In the end, new asymmetric catalysts were used in the reduction of prochiral ketones, giving rise to secondary alcohols with high yields and enantioselectivities. In 2005, the same group designed new squaric amino alcohol pre-catalysts derived from camphor, which were used in the same reduction reaction, but this time with excellent enantioselectivities (Scheme4.1).[8]



Scheme 4.1. Asymmetric reduction of ketones by chiral squaramide ligands.

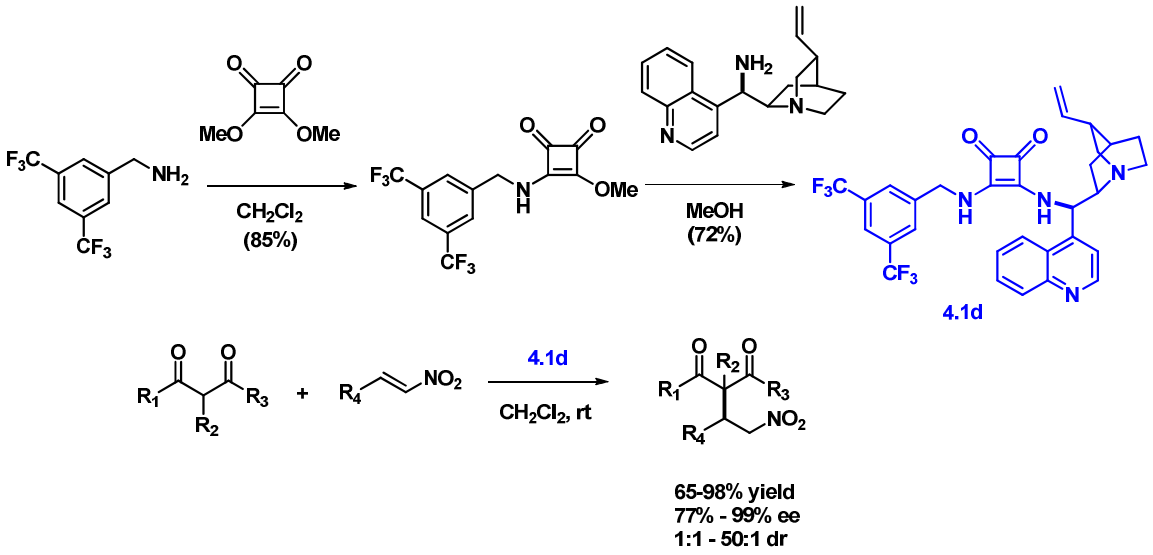
4.1.1.2. Squaramides as Organocatalysts

Since the first use of chiral ureas and thioureas as organocatalysts by Jacobsen, H-bonding asymmetric catalysis has become popular and has developed explosively. In addition to H-bonding activation, the introduction of the

[7] Zhou, H.-B.; Zhang, J.; Lu, S.-M.; Xie, R.-G.; Zhou, Z.-Y.; Choi, M. C. K.; Chan A. S. C.; Yang, T. K. *Tetrahedron* **2001**, *57*, 9325-9333.
[8] Zou, H. H.; Hu, J.; Zhang, J.; You, J. S.; Ma, D.; Lu, D.; Xie, R. G. *J. Mol. Catal. A*, **2005**, *242*, 57-61.

bifunctional catalyst concept to the urea and thiourea catalysts allowed significant advances.[9] In 2008, Rawal *et al.* showed the similarities between squaramides and thioureas in terms of H-bonding ability by using a squaramide organocatalyst for the first time.[6b] After that, like their thiourea analogues, many different chiral scaffolds have been modified to introduce squaramide moieties to be used in various asymmetric transformations. At the same time, the easy and modular synthesis of the squaramides opened a way for the preparation of a wide range of chiral catalysts, and all these benefits made them increasingly popular H-bonding bifunctional catalysts.

Rawal *et al.* first introduced the squaramide organocatalyst with a cinchonine chiral scaffold, completing the synthesis of the catalyst **4.1d** in 2 steps. Then it was used in the conjugate addition of 1,3-dicarbonyl compounds to nitroolefins with great success (Scheme 4.2). The obtained yields and enantioselectivities were comparable to the thiourea counterparts, albeit reactions with **4.1d** were performed with very low catalysts loadings and in shorter times.



Scheme 4.2. Rawal's squaramide organocatalyst synthesis and application in conjugate addition reaction.

The second example of squaramide organocatalyst was presented by Song *et al.* one year after Rawal's example. They used squaramide-based dimeric cinchona alkaloid organocatalysts **4.1e** for the dynamic kinetic resolution (DKR) of

[9] Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc*. **2003**, *125*, 12672-12673.

racemic azlactones.[10] They demonstrated that these dimeric squaramide catalysts have more steric hindrance than their monomeric counterparts. For this reason self-aggregation of the H-bonding catalysts was inhibited and these dimeric species showed very good reactivity and enantioselectivity.

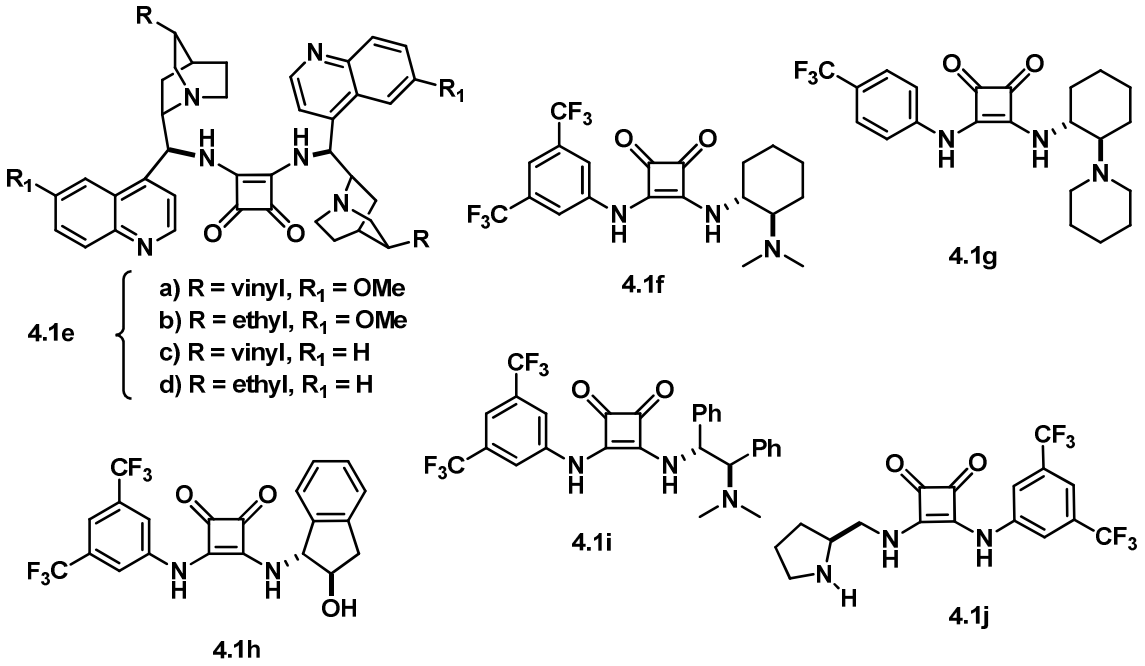
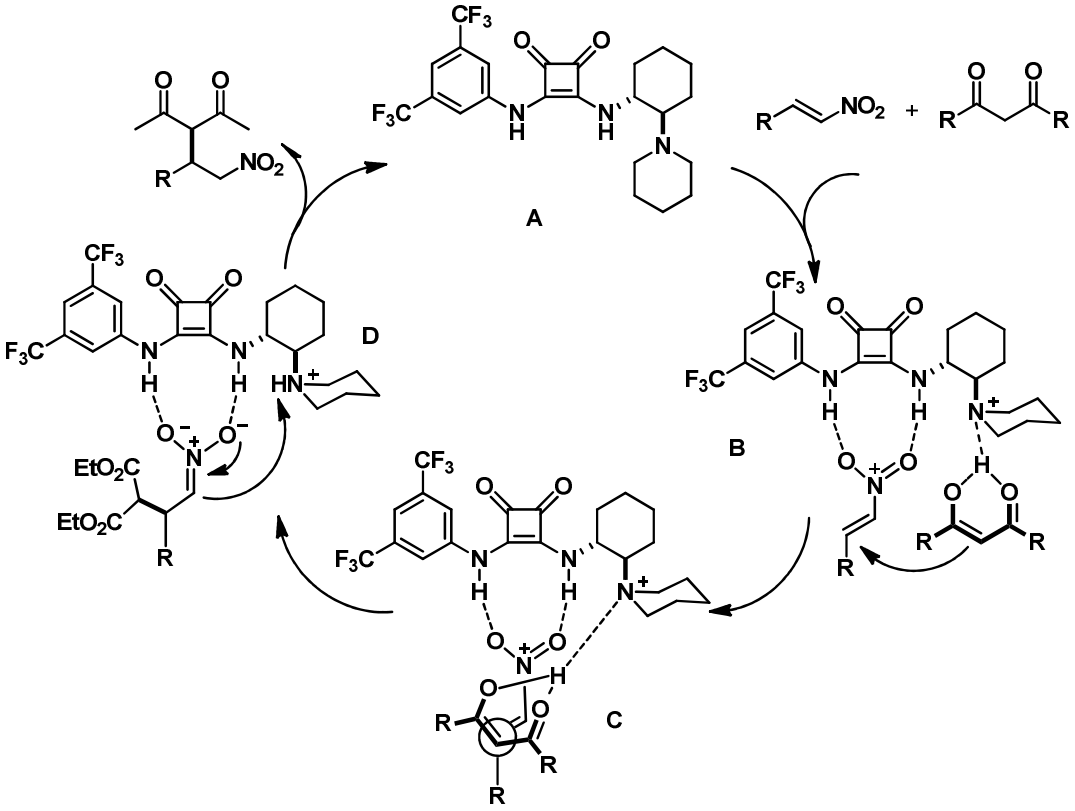


Figure 4.4. Examples from general structures of squaramide organocatalysts.

After that, Rawal's group has continued to synthesize new squaramide derived organocatalysts. They used 1,2-diaminocyclohexane derivatives as a chiral scaffold and they performed the Michael addition of diphenylphosphite to nitroalkenes[11] and Friedel-Crafts reaction of indoles with sulfonylimines[12] with success. It is interesting to see that, in some cases, the squaramide catalyst showed surprisingly higher reactivity compared to the thiourea analogues as in the example of diphenylphosphite addition to nitroalkenes. When this reaction was done with thiourea organocatalysts both yield and enantioselectivity were much lower.[13] However, with squaramide catalyst **4.1g** it was completed in shorter reaction times and with very high yield and ee's.

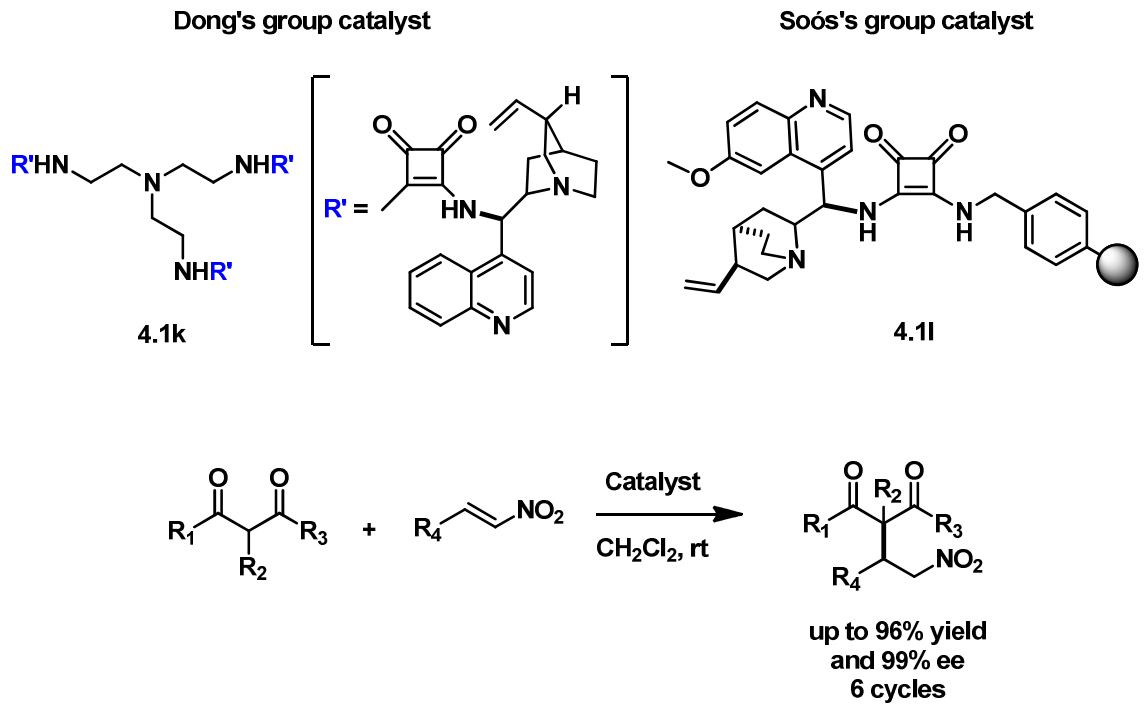
[10] Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 46 7224-7226.
[11] Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 153-156.
[12] Qian, Y.; Ma, G.; Lv, A.; Zhu, H. L.; Zhao, J.; Rawal, V. H. *Chem. Commun*. **2010**, *17*, 3004-3006.
[13] Wang, J.; Heikkinen, L. D.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Wang, W. *Adv. Synth. Catal*. **2007**, *349*, 1052-1056.

The use of squaramide in organocatalysis has become more popular in the last couple of years, and many articles have been published exploiting these asymmetric H-bonding organocatalysts. Most of these studies show that squaramides are well suited catalysts for Michael addition reactions, which is thought to be the result of wider spacing between NH groups, rigid structure of binding units and greater acidity of the NH protons. In the proposed mechanism of Michael addition of 1,3-dicarbonyl compounds to nitroalkenes, the squaramide **A** may act as a bifunctional catalyst. The double H-bonding moiety in squaramide activates the nitroalkene by coordination and the 1,3-dicarbonyl compound is concomitantly deprotonated and activated by the tertiary amine group (**B**). The nucleophilic 1,3-dicarbonyl anion attacks the activated nitroalkene and forms intermediate **C**. In the last step, intermediate **D** abstracts a proton from the ammonium salt and the final product is formed with the release of the catalyst (Scheme 4.3).



Scheme 4.3. Proposed mechanism for the Michael addition.

Since squaramides are stable and robust organocatalysts they have also been used as recyclable catalysts, as pioneered by Dong *et al.*[14] They used squaric acid and cinchonine to form the C_3-symmetrical cinchonine-squaramide organocatalyst **4.1k**, which has been employed in the Michael addition of 1,3-dicarbonyl compounds to nitroolefins. They explained that since their catalyst has poor solubility in organic solvents, its recovery has been done by simple precipitation. C_3-symmetrical cinchonine-squaramide catalyst has been used in recycling experiments with 1 mol% catalyst loading and recycled up to six cycles efficiently with 83% catalyst recovery rate (Scheme 4.4).



Scheme 4.4. C_3-symmetrical cinchonine-squaramide catalyzed Michael addition reaction.

Recently, squaramide organocatalysts have also been immobilized onto aminomethyl-functionalized macroporous and microporous polystyrene supports **4.1l** by Soós *et al.* (Scheme 4.),[15] who performed the same Michael addition reaction as Dong's group. In addition to this they were able to implement immobilized squaramide organocatalysts in a continuous flow application.

In this study we aimed to immobilize squaramide organocatalysts onto polystyrene support in the shortest possible way, without losing the catalytic

[14] Min, C.; Han, X.; Liao, Z.; Wu, X.; Zhou, H. B.; Dong, C. *Adv. Synth. Catal*. **2011**, *353*, 2715-2720.
[15] Kardos, G.; Soós, T. *Eur. J. Org. Chem*. **2013**, *21*, 4490-4494.

activity and selectivity. Thus, a chiral squaramide has been supported onto a polystyrene (PS) resin through a copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction, which was a convenient method for monitoring the immobilization reaction by infrared spectroscopy. We wanted to test the efficiency of our polystyrene (PS) supported squaramide organocatalyst's efficiency in the enantioselective Michael addition reaction of 1,3-dicarbonyl compounds to β-nitrostyrenes under batch conditions and with recycling experiments, then under continuous flow conditions in the Michael addition of 2-hydroxy-1,4-naphtho-quinone to nitroalkenes.

Paper B

A Polystyrene-Supported, Highly Recyclable Squaramide Organocatalyst for the Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to β-Nitrostyrenes

Adv. Synth. Catal. **2012**, *354,* 2905 – 2910

Pinar Kasaplar, Paola Riente, Caroline Hartmann, and

Miquel A. Pericàs

COMMUNICATIONS

DOI: 10.1002/adsc.201200526

A Polystyrene-Supported, Highly Recyclable Squaramide Organocatalyst for the Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to β-Nitrostyrenes

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Abstract: A chiral squaramide has been supported onto a polystyrene (PS) resin through a copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction and used as a very active, easily recoverable and highly reusable organocatalyst for the asymmetric Michael addition of 1,3-dicarbonyl compounds to β-nitrostyrenes. The PS-supported squaramide could be recycled up to 10 times.

Keywords: asymmetric catalysis; catalyst recycling; heterogeneous catalysis; Michael addition; squaramide organocatalysis

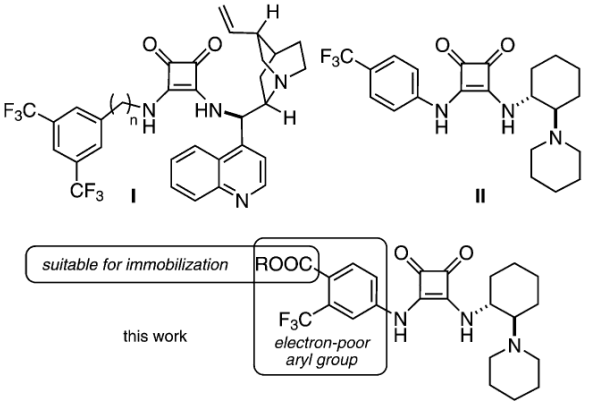


Figure 1. General structures of chiral squaramide-based hydrogen bonding organocatalysts.

The squaramides feature in their structures a rigid four-membered ring with very important electron delocalization. For this reason, they behave as very efficient, directional hydrogen-bond donors.[1] Together with ureas and thioureas, squaramides are privileged members of an important group of molecules widely used for molecular recognition,[2] especially for the recognition of anions. When compared with ureas and thioureas, squaramides differ in some important aspects such as acidity, rigidity, hydrogen bond spacing, and hydrogen bond angle. Probably for these reasons, chiral squaramides have emerged as a promising class of organocatalysts based on non-covalent interactions (Figure 1).[3] From a practical perspective, squaramides present an additional advantage over ureas and thioureas. Thus, while these species normally involve the use of a reactive intermediate (an isocyanate or an isothiocyanate), squaramides are readily available by sequential substitution on stable and commercially available dimethyl squarate. In this manner, highly modular chiral squaramides can be prepared and fine-tuned for specific catalytic applications.[4]

The asymmetric Michael addition is a powerful tool for the C–C bond formation. Starting with the Hajos–Parrish reaction in the early 1970s,[5] the organocatalytic approach to enantiocontrol in the reaction remained opened.[6] Within this group of processes, the addition of 1,3-dicarbonyl compounds to nitrostyrenes[7] depicts particular interest for the rich reactivity of the resulting enantiopure nitro carbonyl products. Enantiocontrol in these reactions has been achieved with organocatalysts based on diamines,[8] amine-thioureas[9] and *Cinchona* derivatives.[10] In fact, the initial application of the squaramide scaffold in organocatalysis, due to Rawal, was in the Michael addition of 1,3-dicarbonyl compounds to nitroolefins, the corresponding adducts being obtained with excellent enantioselectivities.[3a]

While catalytic chemistry is nowadays recognized as a key element in sustainable production, the progressive focus on recycling and reuse has provoked a shift in the interest from homogeneous catalytic species to immobilized ones.[11] When covalent immobilization is considered, ligands and catalysts have to be

properly redesigned to include additional functions allowing bonding to a support without perturbation of the catalytic site. When this condition is met, the inherent advantages of catalytic synthesis are greatly enhanced by the possibility of repeated recovery and reuse.

In spite of its interest and potential, the immobilization of squaramides has not been reported so far.[12] As a continuation of our efforts toward the development of basic toolkits of organocatalysts covalently immobilized either onto polymers[13] or magnetic nanoparticles[14] for batch and continuous flow applications, we report in this communication the first example a chiral squaramide supported onto polystyrene, and its use as a highly efficient and recyclable catalyst for the Michael addition of 1,3-dicarbonyls compounds to β-nitrostyrenes.

For the present study (Figure 1), the chiral scaffold in the squaramide design was specified as (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexanamine (**8**), as this readily available enantiopure material has been previously used with success for squaramide organocatalysis.[3] On the other hand, commercially available 2-trifluoromethyl-4-aminobenzoic acid (**1**) was specified as the source of the electron-poor aryl group in the squaramide design. The carboxy group, ultimately planned for immobilization purposes, was placed in a *para* position with respect to the amino group to ensure a maximal spatial separation between the polymer backbone and the squaramide bifunctional catalyst, thus minimizing transition state perturbation in the catalytic event.[15] The selected immobilization strategy was the CuAAC reaction,[16] and two homogeneous analogues (**9a**, **b**), depicting different spacers between the electron-poor aryl group and the 1,2,3-triazole linker were initially prepared. The catalytic behaviour exhibited by these models helped in the final design of the immobilized squaramide **9c** (Figure 2).

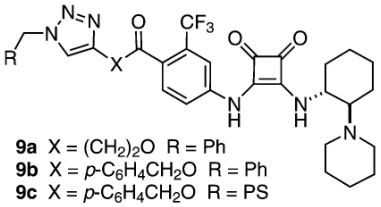
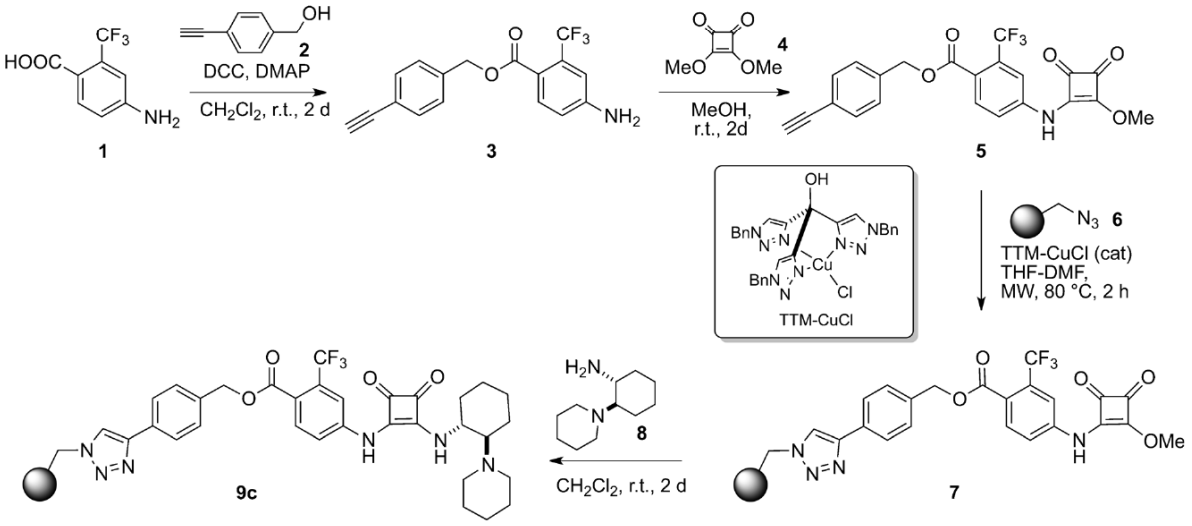


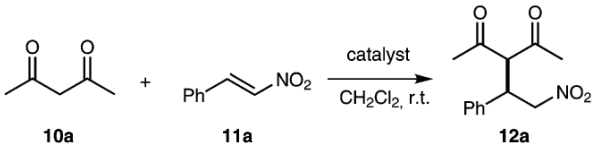
Figure 2. Homogeneous and heterogeneous chiral squaramide organocatalysts in this study.

The target compounds **9a–c** could be readily prepared in four steps from amino acid **1**. The methodology followed for the preparation of PS-supported squaramide **9c** has been summarized in Scheme 1. Model squaramides **9a** and **9b**, in turn, were prepared by analogous sequences in 37% and 51% overall yields, respectively (see the Supporting Information for details). For the preparation of the PS-supported squaramide (**9c**), esterification of **1** with acetylenic alcohol **2** led to ester **3**, suitable for CuAAC immobilization. The squaric acid system was introduced in high yield at this point by reaction with dimethyl squarate **4**, and the so-formed ester-amide **5** was reacted with azidomethyl-polystyrene **6** in the presence of a catalytic amount of TTM-CuCl[17] to afford **7**. The synthesis of the polymer supported squaramide **9c** was completed with the introduction of the chiral scaffold **8**. This particular order of events is the most appropriate one for the preparation of polymer-supported squaramides, since the chiral scaffold is introduced in the last step, and this allows the use of an excess of the chiral moiety (**8**, that can be easily re-



Scheme 1. Synthesis of PS-supported chiral squaramide organocatalyst **9c**.

Table 1. Screening of the catalyst and the catalyst loading for the Michael addition of **10a** to **11a**.[a]



10a **11a** **12a**

Entry	Catalyst (mol%)	Time [h]	Yield [%][b]	*ee* [%][c]
1	**9a** (2.0)	6	94	91
2	**9a** (0.5)	24	89	92
3	**9b** (2.0)	6	93	91
4	**9b** (0.5)	24	92	94
5	**9c** (2.0)	8	88	95
6	**9c** (0.5)	40	62	90
7	**9c** (0.25)[d]	264	83	97
8	**9c** (0.01)[d]	288	41	83

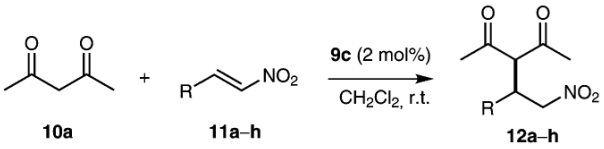
[a] **11a** (1.0 equiv,), **10a** (2.0 equiv.) and **9a–c** in CH_2Cl_2 at room temperature.
[b] Isolated yield.
[c] By HPLC.
[d] At 5 °C.

covered) to ensure the achievement of the highest possible functionalization in the catalytic resin. Starting from a slightly cross-linked (1% DVB) Merrifield resin with $f_0 = 0.52$ mmol g^{-1}, resin **9c** with $f = 0.35$ mmol g^{-1} was obtained.

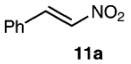
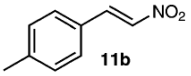
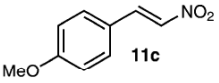
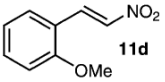
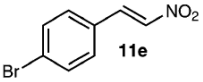
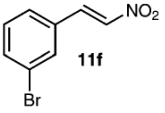
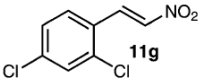
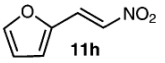
With the catalysts **9a–c** in hand, their activity was tested on the Michael addition of 1,3-diketones (**10**) to nitrostyrenes (**11**). Initially, the reaction between 2,4-pentanedione **10a** with *trans*-β-nitrostyrene **11a** was chosen as a model for the optimization of the catalyst loading and to compare the PS-supported chiral squaramide with its homogeneous analogues (Table 1).

The model catalysts **9a** and **9b** were studied first in order to determine the nature of the optimal spacer. Both catalysts performed equally well at 2 mol% loading at room temperature in dichloromethane (entries 1 and 3), but **9b** led to higher *ee* (94 *vs.* 92%; entries 4 and 2) at 0.5 mol%. For this reason, the longer spacer was selected for the polymer-supported version. Interestingly, the activation provided by the 4-alkoxycarbonyl-3-trifluoromethylphenyl moiety is only slightly lower than that provided by the standard 3,5-bis(trifluoromethyl)phenyl one,[3a] and this validates the design used in the present study. The results obtained with the polymer-supported catalyst **9c** under similar reaction conditions (entry 5 *vs.* entries 1 and 3) were even better, leading to higher *ee* without significant decrease in reaction rate. Interestingly, catalyst loading could be importantly reduced (entries 6–8). When the reaction was carried out with 0.25 mol% **9c** at 5 °C, **12a** was obtained in excellent enantiomeric purity (97% *ee*, entry 7), and even at 0.01 mol% **9c** loading **12a** is obtained in high (83%) enantiomeric purity, albeit at an impractical rate.

Table 2. Michael addition of **10a** to β-nitrostyrenes **11a–h** catalyzed by **9c**.[a]



10a **11a–h** **12a–h**

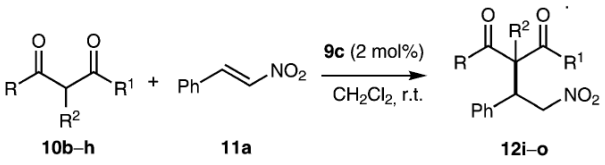
Entry	Nitroolefin	Product	Time [h]	Yield [%][b]	*ee* [%][c]
1	 **11a**	**12a**	8	88	95
2	 **11b**	**12b**	13	87	94
3	 **11c**	**12c**	24	81	92
4	 **11d**	**12d**	13	91	93
5	 **11e**	**12e**	13	87	92
6	 **11f**	**12f**	24	85	87
7	 **11g**	**12g**	13	91	93
8	 **11h**	**12h**	15	91	94

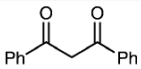
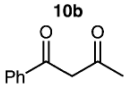
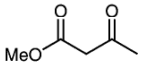
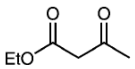
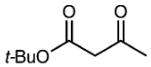
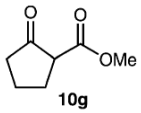
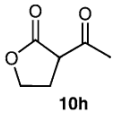
[a] **10a** (0.4 mmol), **11a–h** (0.2 mmol), **9c** (2 mol%) in CH_2Cl_2 (0.6 mL) at room temperature.
[b] Isolated yield.
[c] By HPLC.

The use of catalyst **9c** was next tested in the Michael reaction of a series of β-nitrostyrenes (**11a–h**) with 2,4-pentanedione (**10a**) under the optimal reaction conditions (2 mol%, dichloromethane, room temperature). The results of this study are summarized in Table 2. In general, substrates bearing either *ortho*, *meta* or *para* electron-donating or electron-withdrawing substituents afforded the corresponding Michael adducts with excellent yields and enantioselectivities. Over the full range of studied substrates, the reactivity profile observed for **9c** is very similar to that depicted by the reference system **I** ($n = 1$).[3a]

The catalytic activity of **9c** in the enantioselective Michael reaction of β-nitrostyrene **11a** with a variety of 1,3-dicarbonyl compounds (**10b–h**) was also studied (Table 3). The corresponding conjugate addition ad-

Table 3. Michael addition of 1,3-dicarbonyl compounds **10b–h** to β-nitrostyrene **11a** catalyzed by **9c**.[a]



Entry	NuH	Product	Time [h]	Yield[%][b]/ *dr*[c]	*ee* [%][d]
1	 **10b**	**12i**	20	56	86
2	 **10c**	**12j**	9	88/1:1.1	92 (90)
3	 **10d**	**12k**	16	98/(1:1)	89 (89)
4	 **10e**	**12l**	24	85/(1:1)	93 (92)
5	 **10f**	**12m**	60	60/2.2:1	89 (91)
6	 **10g**	**12n**	24	89/29:1	96 (87)
7	 **10h**	**12o**	24	62/5:1	83 (88)

[a] **10b–h** (0.4 mmol), **11a** (0.2 mmol) **9c** (2 mol%) in CH_2Cl_2 (0.6 mL) at room temperature.
[b] Isolated yield.
[c] By ^{1}H NMR.
[d] By HPLC; *ee*s of the minor diastereomers in parenthesis.

ducts were obtained with good to excellent yields. For acyclic 1,3-dicarbonyls, diastereoselectivity was low to moderate (entries 2–5) in agreement with previous reports.[3a] For cyclic substrates (entries 6–7) higher diastereoselectivities were recorded. Enantioselectivity in these reactions followed the same trend observed in Table 2. Thus, values around 90% *ee* were uniformly observed, 4.0% below (mean value) those observed with the reference, homogeneous system.[3a]

As mentioned above, the ultimate reason for the immobilization of homogeneous catalysts is to open a simple way for recovery (by simple filtration) and reuse, thus upgrading the sustainability characteristics of the processes where the considered catalysts act. The recyclability of **9c** was studied in the reaction of

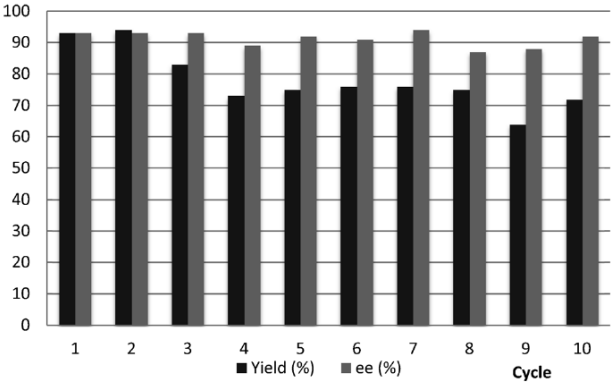


Figure 3. Recycling of **9c** in the asymmetric addition of **10a** to **11a**.

10a with **11a** as model substrates. Ten consecutive reaction cycles were performed in dichloromethane at room temperature with a single catalyst sample, initially representing 4 mol% of the limiting **11a** reactant. Reaction time was arbitrarily fixed to 6 h, and reaction product (**12a**) in every individual cycle was isolated and purified for yield calculation. After each cycle, the catalyst was separated by filtration, washed, dried and reused. The results of this study have been represented in Figure 3, where data for every individual cycle represent the average value of two independent experiments.

Very gratifyingly, enantioselectivity is preserved along the ten-cycle experiment. Conversion, in turn, suffers some deterioration, but remains high (>70%) over the whole series. The joint behaviour of enantioselectivity and conversion is typical for situations where the catalyst is chemically stable, but stirring provokes some etching in the beads of the immobilized catalyst leading to a decrease in the effective catalyst loading as the series of experiments progresses.[18] With sufficiently active immobilized catalysts, this phenomenon can be suppressed by performing the reactions in continuous flow mode.[13a,19]

In conclusion, we have reported the first example of a chiral squaramide organocatalyst covalently immobilized onto a polystyrene (Merrifield type) resin. A CuAAC immobilization strategy has been implemented involving short, simple and high yielding steps from readily available precursors. The functional resin prepared in this way has been applied to the asymmetric Michael addition of 1,3-dicarbonyl compounds to β-nitrostyrenes with good to excellent yields and enantioselectivities. The 1,2,3-triazole linker provides the immobilized squaramide with excellent catalytic stability, thus allowing its successful recovery and reuse in 10 consecutive reaction cycles.

Experimental Section

Experimental Procedure for Michael Reactions

To a suspension of squaramide organocatalyst **9c** (2 mol%) in CH_2Cl_2 (0.6 mL), the nitroolefin **11** (0.2 mmol) and the 1,3-dicarbonyl compound **10** (0.4 mmol) were added at room temperature. The reaction mixture was magnetically stirred at room temperature and monitored by TLC until complete conversion of the starting material. The resultant suspension was filtered, the resin was washed twice with CH_2Cl_2 on the same filter, and the filtrate was concentrated under reduced pressure and purified by column chromatography (silica gel, hexane/EtOAc) to give the pure Michael adduct.

Recycling of 9c

trans-β-Nitrostyrene (**11a**) (45 mg, 0.3 mmol) and catalyst **9c** (34.2 mg, $f = 0.35$ mmol g^{-1}, 4 mol%) were mixed with 2.4-pentanedione (**10a**) (60 μL, 0.6 mmol) in CH_2Cl_2 (0.9 mL). The suspension was stirred at room temperature for 6 h and then directly filtered. The solid resin was washed twice with CH_2Cl_2 and the organic filtrate was concentrated under reduced pressure. The addition product, **12a**, was purified by column chromatography and the functional resin **9c** was dried overnight under vacuum and directly used in the next reaction cycle.

Acknowledgements

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A Polystyrene-Supported, Highly Recyclable Squaramide Organocatalyst for the Enantioselective Michael Addition of 1,3-Dicarbonyl Compounds to β-Nitrostyrenes

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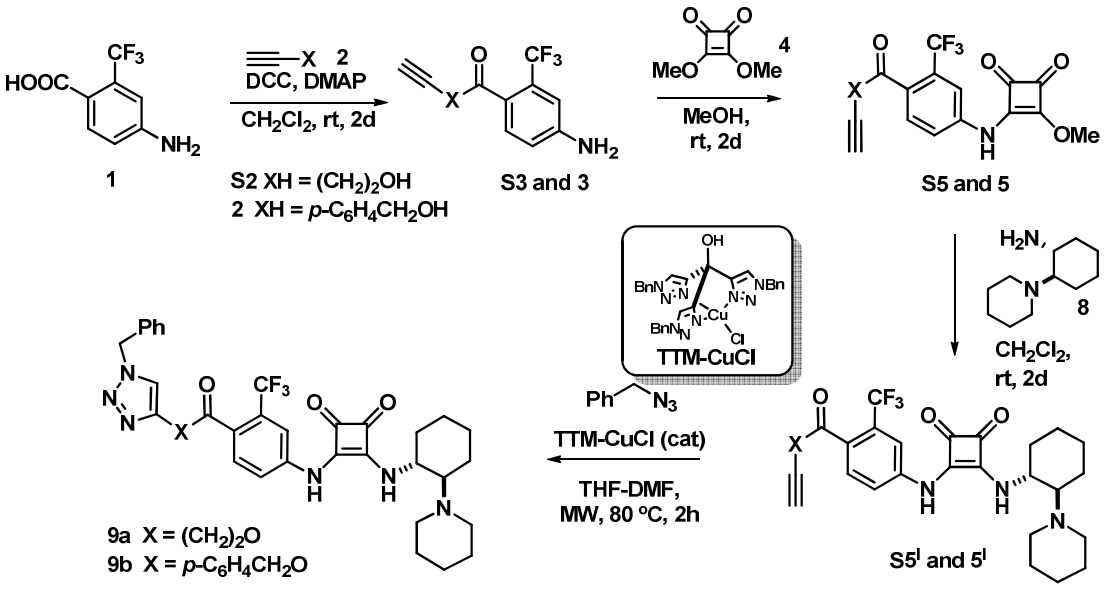
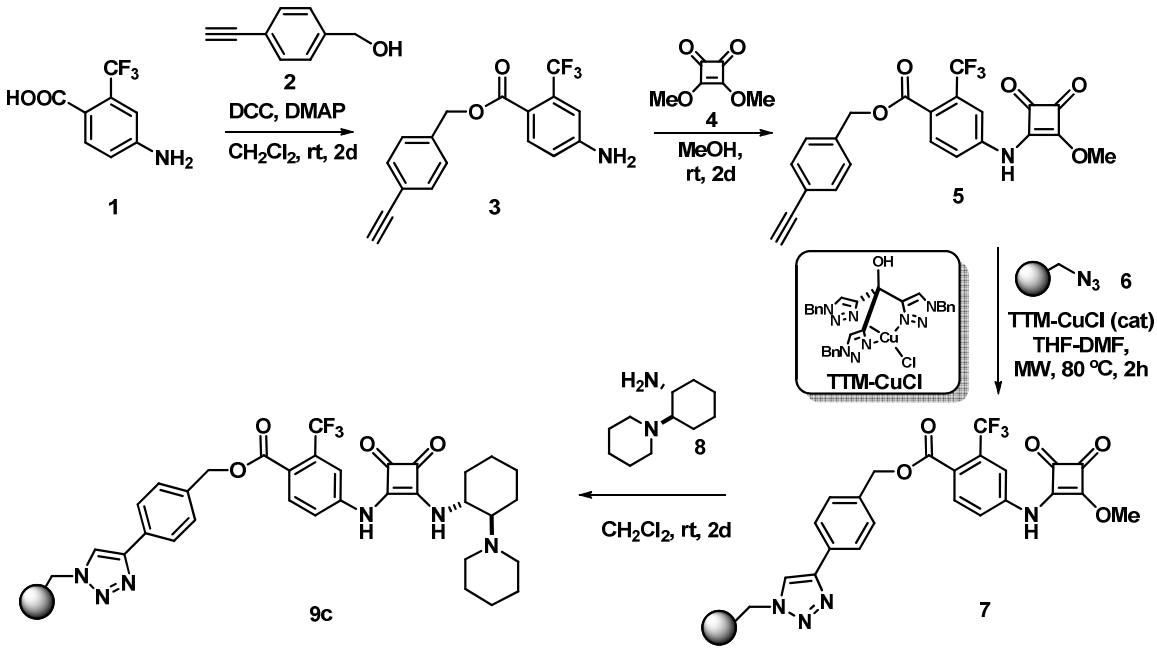
General Methods:

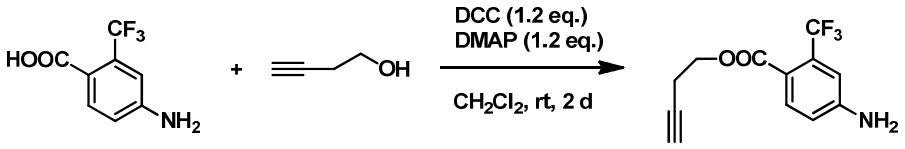
Unless otherwise stated, all commercial reagents were used as received and all reactions were carried out directly under open air. Merrifield resin (1% DVB, f = 0.53 mmol Cl g^{-1} resin) was obtained from Novabiochem. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H or at 100 MHz and 125 MHz for ^{13}C, respectively. TMS was used as internal standard for ^{1}H-NMR and $CDCl_3$ for ^{13}C-NMR. Chemical shifts are reported in ppm referred to TMS. FT-IR measurements carried out on a Bruker Optics FTIR Alpha spectrometer equipped with a DTGS detector, KBr beamsplitter at $4cm^{-1}$ resolution. Elemental analyses were performed on a LECO CHNS 932 micro-analyzer at the Universidad Complutense de Madrid, Spain. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier Instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Specific optical rotation measurements were carried out on a Jasco P-1030 model polarimeter equipped with a PMT detector using the Sodium line at 589 nm. The experiments under microwave irradiation were carried out in a CEM Discover microwave reactor. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralpak AD-H, OD-H and AS-H columns and guard columns. Racemic standard products were prepared using DABCO (10 mol%) as catalyst in order to establish HPLC conditions. Melting points (mp) are uncorrected and were recorded on a Buchi Melting Point B-540 melting point apparatus. Compound **8** was synthesized according to the reported procedures. [1]

Synthesis of the Homogeneous Catalysts 9a and 9b



Synthesis of the PS-Supported Catalysts 9c





S3

But-3-yn-1-yl 4-amino-2-(trifluoromethyl)benzoate (S3)

N,N'-Dicyclohexylcarbodiimide (0.42 g, 2.05 mmol) and 4-dimethylaminopyridine (0.35 g, 2.05 mmol) were dissolved in CH_2Cl_2 (11 mL) in a reaction flask. Then 4-amino-2-(trifluoromethyl)benzoic acid (0.35 g, 1.7 mmol) was added and continued to stirring at room temperature for 30 minutes. Finally, 3-butyn-1-ol (0.14 g, 2.05 mmol) was added over reaction mixture under argon atmosphere and stirred at room temperature for 2 days. After completion of the reaction, mixture was filtered and filtrate was concentrated. Product was isolated by column chromatography on silica gel with CH_2Cl_2/MeOH (98:2) eluent. The product was obtained as a light yellow solid with 84 % yield.

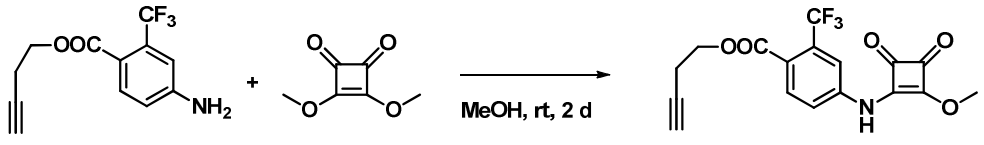
m.p.: 95-97 ^{o}C

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.01 (t, 1H), 2.64 (dt, *J* = 2.66, 6.93 Hz, 2H), 4.22 (br s, 2H), 4.38 (t, 2H), 6.76 (dd, *J* = 2.34, 8.46 Hz, 1H), 6.98 (d, *J* = 2.36 Hz, 1H), 7.79 (d, *J* = 8.48 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.62, 149.72, 133.67, 124.63, 121.91, 118.58, 115.78, 112.82, 112.75, 112.69, 80.02, 69.93, 62.84, 18.83.

HRMS (ESI+): *m/z* = 280.0556, calcd. for $C_{12}H_{10}NO_2F_3Na[M+Na]^+$, found 280.0561.

IR (ATR): ν = 3470, 3371, 3292, 3232, 1704, 1635, 1606, 1571, 1454, 1347, 1272, 1244, 1164, 1136, 1041, 1006, 917cm^{-1}.



S5

But-3-yn-1-yl-4-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-2 (trifluoromethyl)benzoate (S5)

A mixture of but-3-yn-1-yl 4-amino-2-(trifluoromethyl)benzoate (0.30 g, 1.16 mmol) and 3,4-dimethoxycyclobut-3-ene-1,2-dione (0.16 g, 1.17 mmol) in 2.8 ml MeOH was stirred at room temperature for 2 days. Product was obtained by filtration as yellow solid with 70 % yield.

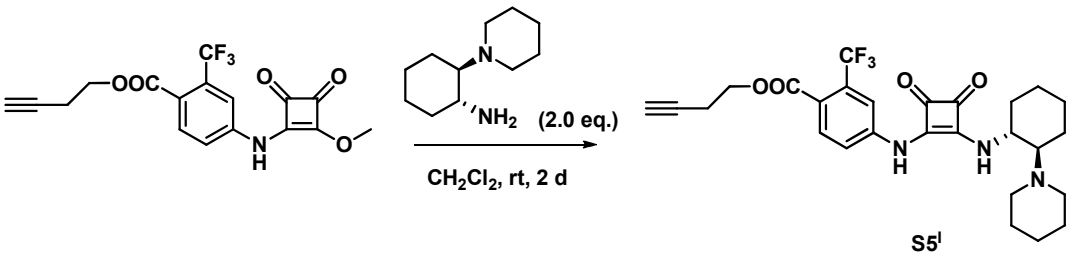
m.p.: > 190 ^{o}C decomp.

^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.63 (t, *J* = 6.44 Hz, 2H), 2.89 (t, *J* = 2.60 Hz, 1H), 4.33 (t, *J* = 6.44 Hz, 2H), 4.41 (s, 3H), 7.72 (m, 1H), 7.94 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): 188.07, 185.31, 165.32, 141.87, 132.74, 129.36, 129.08, 124.58, 124.46, 122.39, 122.16, 117.57, 81.09, 73.10, 63.78, 61.39, 18.95.

HRMS (ESI+): *m/z* = 390.0553, calcd. for $C_{17}H_{12}NO_5F_3Na[M+Na]^+$, found 390.0565.

IR (ATR): ν = 3288, 3181, 3091, 3016, 1804, 1705, 1606, 1567, 1529, 1443, 1290, 1137, 895 cm^{-1}.



But-3-yn-1-yl 4-((3,4-dioxo-2-(((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)amino) cyclobut-1-en-1-yl)amino)-2-(trifluoromethyl)benzoate (S5^{I})

A mixture of but-3-yn-1-yl 4-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-2-(trifluoromethyl)benzoate (0.25 g, 0.68 mmol) and (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexanamine (0.24 g, 1.36 mmol) in CH_2Cl_2 (3 mL) was stirred at room temperature for 2 days. When the reaction was complete excess solvent was evaporated and product was isolated by column chromatography, as an eluent CH_2Cl_2/MeOH (20:1) was used and product obtained as orange foam, with 77 % yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.20-1.49 (m, 4H), 1.50-1.69 (m, 3H), 169-1.84 (m, 3H), 1.85-2.00 (m, 3H), 2.05 (t, *J* = 2.64 Hz, 1H), 2.10 (d, *J* = 12.20 Hz, 1H), 2.23

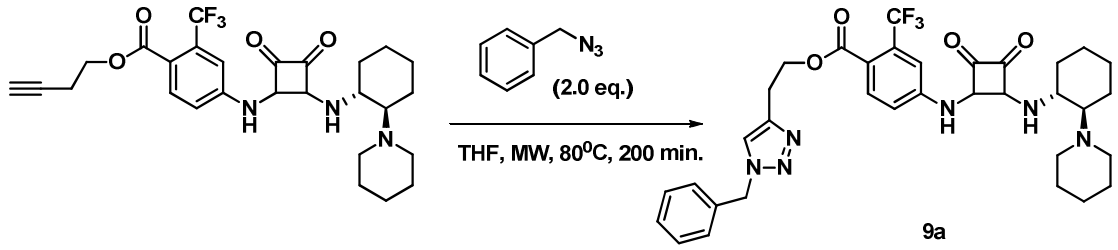
(d, *J* = 12.00 Hz, 1H), 2.65 (dt, *J* = 2.64, 6.96 Hz, 2H), 2.78-2.89 (m, 2H), 3.04-3.31 (m, 3H), 4.07- 4.17 (m, 1H), 4.39 (t, *J* = 6.92 Hz, 2H), 7.61-7.75 (m, 2H), 7.97 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 183.67, 180.76, 170.11, 165.26, 163.78, 141.90, 132.85, 124.11, 123.56, 121.93, 120.25, 116.20, 79.76, 70.16, 68.51, 63.14, 54.16, 50.36, 34.21, 24.48, 24.29, 23.66, 23.04, 18.76.

HRMS (ESI+): *m/z* = 518.2265, calcd. for $C_{27}H_{31}N_3O_4F_3[M+H]^+$, found 518.2267.

IR (ATR): ν = 3272, 2930, 2855, 1794, 1724, 1661, 1614, 1576, 1535, 1443, 1384, 1323, 1279, 1107 cm^{-1}.

$[\alpha]_D^{27}$ = –22.59 (c = 0.61 in MeOH).



2-(1-benzyl-1H-1,2,3-triazol-4-yl)ethyl-4-((2,3-dioxo-4-(((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl) amino)cyclobutyl)amino)-2-(trifluoromethyl)benzoate (9a)

But-3-yn-1-yl 4-((3,4-dioxo-2-(((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)amino)-cyclobut-1-en-1-yl)amino)-2-(trifluoromethyl) benzoate (0.20 g, 0.38 mmol), benzyl azide (0.10 g, 0.8 mmol), 3 mL of THF and tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol·CuCl catalyst [2] (0.008 g, 0.013 mmol, 3 mol%) were placed in a tube for microwave reactor. The reaction mixture was heated at 80 ºC for 200 min under microwave irradiation of 200 W by stirring. After reaction was completed, the product was isolated by column chromatography, as an eluent CH_2Cl_2/MeOH (20:1) was used. Product was obtained as orange foam with 82 % yield.

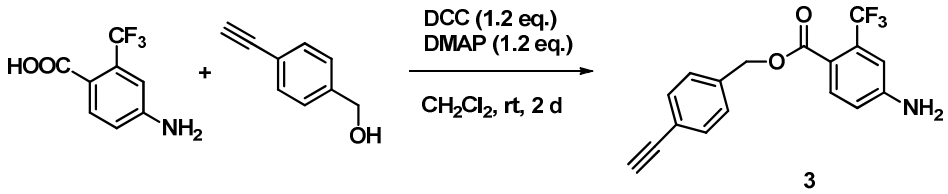
^{1}H-NMR (500 MHz, $CDCl_3$, 328K): 1.19-1.62 (m, 6H), 1.63-1.93 (m, 6H), 2.04-2.07 (m, 1H), 2.22-2.24 (m, 1H), 2.68-3.12 (br, 3H), 3.12 (t, *J* = 6.6 Hz, 3H), 4.11 (br, 1H), 4.51 (t, *J* = 6.6 Hz, 3H), 5.48 (s, 2H), 7.22-7.24 (m, 2H), 7.28-7.31 (m, 3H), 7.41 (s, 1H), 7.52-7.63 (m, 2H), 7.88 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, 328K): 184.00, 180.87, 165.47, 144.30, 141.93, 134.91, 132.41, 130.66, 130.41, 130.09, 128.97, 128.59, 127.96, 124.14, 123.89, 121.89, 120.39, 116.38, 68.67, 64.36, 54.40, 54.02, 34.37, 25.29, 24.60, 24.29, 23.72, 23.16.

HRMS (ESI+): *m/z* = 651.2905, calcd. for $C_{34}H_{38}N_6O_4F_3[M+H]^+$, found 651.2907.

$[\alpha]_D^{26}$= –28.54 (c = 0.98 in $CHCl_3$).

IR (ATR): ν = 2932, 2858, 1791, 1729, 1694, 1605, 1581, 1538, 1426, 1330, 1284, 1258, 1168, 1133, 1044, 908, 726 cm^{-1}.



3

4-ethynylbenzyl 4-amino-2-(trifluoromethyl)benzoate (3)

N,N'-Dicyclohexylcarbodiimide (0.905 g, 4.4 mmol) and 4-Dimethylaminopyridine (0.536 g, 4.4 mmol) were dissolved in CH_2Cl_2 (23 mL) in a reaction flask. Then 4-amino-2-(trifluoromethyl)benzoic acid (0.75 g, 3.7 mmol) was added and continued to stirring at room temperature for 30 minutes. Finally, 3-butyn-1-ol (0.518 g, 4.4 mmol) was added over reaction mixture under argon atmosphere and stirred at room temperature for 2 days. After completion of the reaction, mixture was filtered and filtrate was concentrated. Product was isolated by column chromatography on silica gel with CH_2Cl_2/Methanol (98:2) eluent. The product was obtained as a white solid with 80% yield.

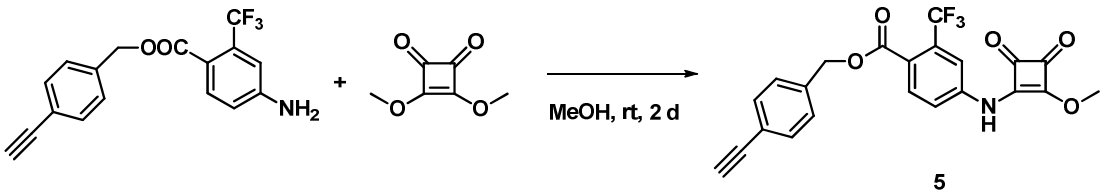
m.p.: 123-124^{o}C

^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.14 (s, 1H), 5.24 (s, 1H), 6.34 (s, 2H), 6.77 (dd, *J* = 2.32, 8.60 Hz, 1H), 7.00 (d, *J* = 2.28 Hz, 1H), 7.45 (m, 4H), 7.73 (d, *J* = 8.60 Hz, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 165.13, 153.06, 137.50, 134.14, 132.25, 130.43, 130.12, 128.65, 125.33, 121.78, 115.23, 114.49, 111.98, 111.92, 83.66, 81.36, 65.98.

HRMS (ESI+): *m/z* = 342.0730, calcd. for $C_{17}H_{12}NO_2F_3Na[M+Na]^+$, found 342.0718.

IR (ATR): ν = 3429, 3338, 3277, 2118, 1719, 1630, 1453, 1341, 1271, 1249, 1132, 1042, 825.5 cm^{-1}.



5

4-ethynylbenzyl 4-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-2 (trifluoromethyl) benzoate (5)

A mixture of 4-ethynylbenzyl 4-amino-2-(trifluoromethyl)benzoate (0.80 g, 2.50 mmol) and 3,4-dimethoxycyclobut-3-ene-1,2-dione (0.35 g, 2.50 mmol) in 5 mL MeOH was stirred at room temperature for 2 days. Product was obtained by filtration as yellow solid with 81 % yield.

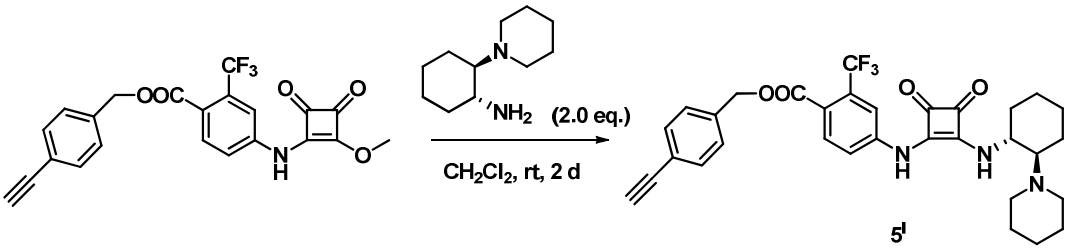
m.p.: 169-171 ^oC

^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.17 (s, 1H), 4.18 (s, 1H), 4.40 (s, 3H), 5.33 (s, 2H), 7.46 (m, 4H), 7.69 (m, 1H), 7.92 (m, 2H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 187.78, 185.10, 180.45, 169.47, 165.30, 142.00, 136.77, 132.91, 132.28, 129.35, 129.04, 128.87, 124.80, 124.30, 122.17, 122.04, 117.59, 83.60, 81.55, 67.01, 61.37, 49.05.

HRMS (ESI+): *m/z* = 452.0471, calcd. for $C_{22}H_{14}NO_5F_3Na$ $[M+Na]^+$, found 452.0722.

IR (ATR): ν = 3534, 3309, 3087, 3006, 1800, 1711, 1603, 1576, 1524, 1382, 1262, 1131 cm^{-1}.



4-ethynylbenzyl 4-((3,4-dioxo-2-(((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)amino)-cyclobut-1-en-1-yl)amino)-2-(trifluoromethyl)benzoate (5^{I})

A mixture of 4-ethynylbenzyl 4-((2-methoxy-3,4-dioxocyclobutyl)amino)-2-(trifluoromethyl)benzoate (0.62 g, 1.46 mmol) and (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexanamine (0.53 g, 2.92 mmol) in 7.5 mL CH_2Cl_2 was stirred at room temperature for 2 days. When the reaction was complete excess solvent was evaporated and product was isolated by column chromatography. As an eluent CH_2Cl_2/MeOH (20:1) was used and product obtained as yellow-orange foam, with 85% yield.

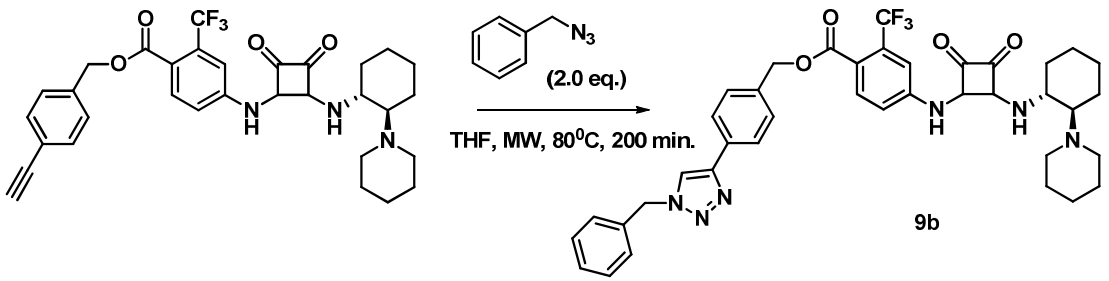
^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.10-1.23(m, 1H), 1.24-1.34 (m, 2H), 1.35-1.55 (m, 5H), 1.55-1.67 (m, 1H), 1.67-1.76 (m, 1H), 1.76-1.87 (m, 1H), 1.89-2.02 (m, 1H), 2.14-2.24 (m, 1H), 2.37-2.72 (m, 3H), 2.73-2.99 (m, 2H), 3.10 (s, 1H), 4.04 (br s, 1H), 5.29 (s, 2H), 7.36 (d, *J*= 8.15 Hz, 2H), 7.49 (d, *J*= 8.15 Hz, 2H), 7.67-7.69 (m, 1H), 7.75-7.76 (m, 1H), 7.98 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 183.87, 181.06, 165.26, 142.25, 136.16, 132.77, 132.31, 130.68, 130.40, 128.21, 124.15, 123.84, 122.11, 121.96, 120.67, 116.82, 83.17, 77.73, 68.45, 66.85, 53.45, 34.15, 25.60, 24.81, 24.49, 23.68.

HRMS (ESI+): *m/z* = 580.2432, calcd. for $C_{32}H_{33}N_3O_4F_3$ $[M+H]^+$, found 580.2423.

IR (ATR): ν = 3241, 2934, 2858, 1790, 1733, 1604, 1574, 1537, 1426, 1328, 1281, 1239, 1137, 1103, 1018, 822 cm^{-1}.

$[\alpha]_D^{26}$= –73.32 (c = 1.09 in $CHCl_3$).



4-(1-benzyl-1H-1,2,3-triazol-4-yl)benzyl-4-((2,3-dioxo-4-(((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl) amino)cyclobutyl)amino)-2-(trifluoromethyl)benzoate (9b)

4-ethynylbenzyl 4-((3,4-dioxo-2-(((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)amino)-cyclobut-1-en-1-yl)amino)-2-(trifluoromethyl) benzoate (0.23 g, 0.41 mmol), benzyl azide (0.10 g, 0.81 mmol), 4 mL of THF and tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol·CuCl catalyst [2] (0.005 g, 0.013 mmol, 3 mol%) were placed in a tube for microwave reactor. The reaction mixture was heated at 80 ºC for 200 min under microwave irradiation of 200 W by stirring. After reaction was completed, the product was isolated by column chromatography, as an eluent CH_2Cl_2/MeOH (20:1) was used. Product was obtained as pink-orange foam with 93 % yield.

^{1}H-NMR (400 MHz, $CDCl_3$, 328K): δ 1.12-1.35(m, 3H), 1.36-1.51 (m, 3H), 1.57 (br, 2H), 1.63-1.86 (m, 4H), 1.95-1.96 (m, 1H), 2.16-2.18 (m, 1H), 2.57-3.08 (m, 4H), 4.05 (br s, 1H), 5.24 (s, 2H), 5.54 (s, 2H), 7.20-7.44 (m, 7H), 7.65(br s, 2H), 7.69-7.80 (m, 3H), 7.89 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, 328K): δ 184.06, 180.90, 165.46, 147.79, 142.13, 135.56, 134.71, 132.67, 130.70, 130.31, 129.12, 128.79, 128.07, 125.97, 124.26, 123.93, 122.03, 120.51, 120.05, 116.57, 68.67, 67.03, 54.61, 54.28, 34.43, 24.84, 24.60, 24.29, 23.73, 23.28.

HRMS (ESI+): *m/z* = 713.3054, calcd. for $C_{39}H_{40}N_6O_4F_3$ $[M+H]^+$, found 713.3063.

IR (ATR): ν = 2929, 2856, 1790, 1729, 1690, 1579, 1537, 1495, 1424, 1374, 1283, 1240, 1135, 1107, 1018 cm^{-1}.

$[\alpha]_D^{26}$= –44.83 (c = 0.99 in $CHCl_3$).

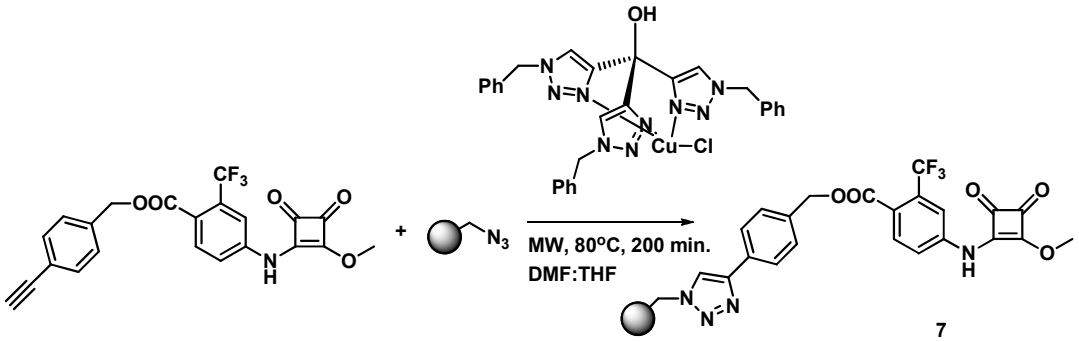
6

Azidomethylpolystyrene (6)

Sodium azide (1.03 g, 15.9 mmol) was added to a suspension of 6 g of chloromethylpolystyrene (f = 0.53 mmol g-1) in 60 mL of DMF. The mixture was shaken (orbital shaker) at 60 ºC for 20 h. After cooling, the suspension was filtered and the resin was sequentially washed with water (500 mL), THF (250 mL), THF-MeOH 1:1 (250 mL), MeOH (250 mL) and THF (250 mL). The solid was dried in vacuo for 24 h at 40 ºC.

A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.2; found: N 2.22, C 89.02, H 7.63; *f* = 0.528 mmol g^{-1}.

IR (ATR): ν = 2094 cm^{-1}.



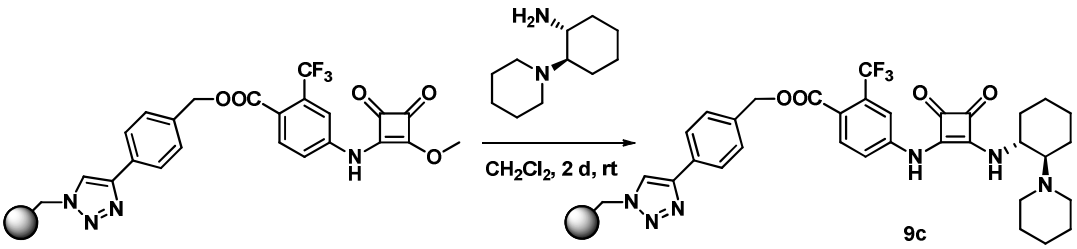
7

4-(1-ethyl-1H-1,2,3-triazol-4-yl)benzyl 4-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-2-(trifluoromethyl)benzoate polystyrene (7)

4-ethynylbenzyl 4-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-2 (trifluoro-methyl)benzoate (100 mg, 0.23 mmol), azidomethylpolystyrene resin (370 mg, *f* = 0.528 mmol g^{-1}), 2 mL of DMF, 2 mL of THF and *TTM.*CuCl catalyst [2] (0.005 g, 0.006 mmol, 3 mol %) were placed in a tube for microwave reactor. The reaction mixture was heated at 80 ºC for 200 min under microwave irradiation of 200 W without stirring. After the reaction was completed, the resin was filtered and washed with DMF (200 mL), H_2O (200 mL), THF (200 mL), MeOH (200 mL), and THF (200 mL) again. The resin was dried overnight in vacuo at 40 ºC.

IR (ATR): ν = 3059, 3024, 2920, 1802, 1727, 1599, 1492, 1450, 1284, 749, 695 cm^{-1}.

A 99% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.41; found: C 85.27, H 7.26, N 2.38; *f* = 0.425 mmol g^{-1}.



4-(1-ethyl-1H-1,2,3-triazol-4-yl)benzyl 4-((3,4-dioxo-2-(((1*R*,2*R*)-2-(piperidin-1yl)cyclohexyl)amino)cyclobut-1-en-1-yl)amino)-2-(trifluoromethyl)benzoate polystyrene (9c)

A mixture of 4-(1-ethyl-1H-1,2,3-triazol-4-yl)benzyl 4-((2-methoxy-3,4-dioxocyclobut-1-en-1-yl)amino)-2-(trifluoromethyl)benzoate polystyrene (*f* = 0.425 mmol.g^{-1}) (350 mg, 0.148 mmol) and (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexanamine (0.054 g, 0.29 mmol) in CH_2Cl_2 (4mL) was shake at room temperature. After 2 days, the reaction mixture was filtered and resin was washed with DMF (200 mL), H_2O (200 mL), THF (200 mL), MeOH (200 mL), and THF (200 mL). The resin was dried overnight in vacuo at 40 ºC.

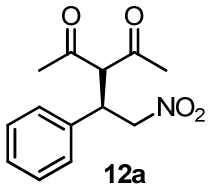
IR (ATR): ν = 3060, 3024, 2919, 2851, 1791, 1733, 1599, 1539, 1491, 1450, 1373, 1140, 752, 694 cm^{-1}.

A 90% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 2.95; found: C 84.52, H 7.32, N 2.95; *f* = 0.351 mmol g^{-1}.

Typical procedure for the Michael reaction

To a solution of squaramide organocatalyst **9c** (11.5 mg, 0.004 mmol) in CH_2Cl_2 (0.6 mL) was added nitroolefin (0.2 mmol) and 1,3-dicarbonyl compound (0.4 mmol). Reactions were monitored by TLC with the consumption of nitroolefin the reaction mixture was concentrated and purified by column chromatography to afford the Michael product.

Physical and spectroscopic data for Michael adducts

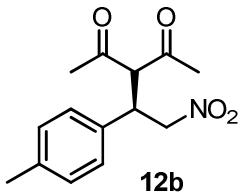


12a

(*R*)-3-(2-nitro-1-phenylethyl)pentane-2,4-dione (12a) [3] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 92% yield. HPLC with Chiralcel OD-H column (Hexanes/EtOH, (95:5), 1.0 ml/min, 210 nm): t_{minor} = 24.0 min, t_{major} = 25.8 min, 94 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.28 (s, 3H), 4.26-4.22 (m, 1H), 4.37 (d, *J* = 10.7 Hz, 1H), 4.67-4.61 (m, 2H), 7.19-7.17 (m, 2H), 7.34-7.26 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.75, 201.02, 136.02, 129.33, 128.54, 127.95, 78.17, 70.67, 42.79, 30.44, 29.60.

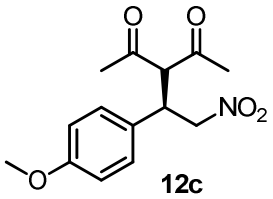


12b

(*R*)-3-(2-nitro-1-(p-tolyl)ethyl)pentane-2,4-dione (12b) [4] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 87 % yield. HPLC with Chiralcel AD-H column (Hexanes: isopropanol, (90:10), 1ml/min, 230 nm) t_{minor} = 10.7 min, t_{major} = 17.3 min, 94 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.28 (s, 3H), 2.29 (s, 3H), 4.22-4.17 (m, 1H), 4.34 (d, *J* = 10.8 Hz, 1H), 4.61-4.57 (m, 2H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.88, 201.13, 138.35, 132.84, 130.16, 129.99, 127.79, 78.36, 70.81, 42.46, 30.41, 29.47, 21.06.

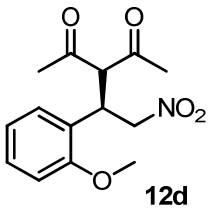


12c

(*R*)-3-(1-(4-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (12c) [4] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 81% yield. HPLC with Chiralcel AD-H column (Hexanes:isopropanol, (80:20), 0.8ml/min, 210 nm) t_{minor} = 11.5 min, t_{major} = 16.5 min, 92 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.98 (s, 3H), 2.28 (s, 3H), 3.73 (s, 3H), 4.21-4.17 (m, 1H), 4.33 (d, *J* = 10.9 Hz, 1H), 4.59-4.58 (m, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 201.88, 201.15, 159.53, 129.07, 127.65, 114.70, 78.45, 70.94, 55.23, 42.13, 30.37, 29.44.

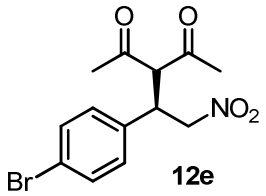


12d

(*R*)-3-(1-(2-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (12d) [4] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 91 % yield. HPLC with Chiralcel OD-H column (Hexanes:isopropanol, (85:15), 0.5 ml/min, 210 nm) t_{minor} = 25.0 min, t_{major} = 26.0 min, 93 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H), 2.26 (s, 3H), 3.87 (s, 3H), 4.50-4.45 (m, 1H), 4.60-4.56 (m, 2H), 4.78 (dd, *J* = 12.5, 8.0 Hz, 1H), 6.89-6.87 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.27-7.24 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): *δ* 202.30, 201.57, 157.03, 130.24, 129.76, 123.54, 121.18, 111.25, 76.56, 69.02, 55.45, 38.95, 30.44, 28.75.

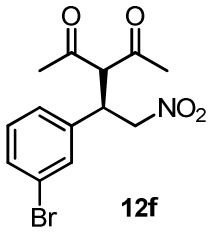


12e

(*R*)-3-(1-(4-bromophenyl)-2-nitroethyl)pentane-2,4-dione (12e) [4] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 87% yield. HPLC with Chiralcel AS-H column (Hexanes:isopropanol, (85:15), 1.0 ml/min, 210 nm) t_{minor} = 17.9 min, t_{major} = 32.9 min, 92 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.97 (s, 3H), 2.29 (s, 3H), 4.24-4.19 (m, 1H), 4.32 (d, *J* = 10.7 Hz, 1H), 4.61-4.60 (m, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.37, 200.54, 135.10, 132.52, 129.63, 122.69, 77.84, 70.46, 42.20, 30.44, 29.68.

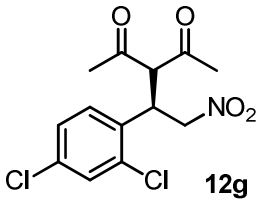


12f

(*R*)-3-(1-(3-bromophenyl)-2-nitroethyl)pentane-2,4-dione (12f) [5] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 85% yield. HPLC with Chiralcel AD-H column (Hexanes:isopropanol, (95:5), 1.0 ml/min, 230 nm) t_{minor} = 18.6 min, t_{major} = 20.4 min, 87 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.00 (s, 3H). 2.29 (s, 3H), 4.20 (ddd, *J* = 10.5, 7.8, 4.8 Hz, 1H), 4.34 (d, *J* = 10.6 Hz, 1H), 4.63-4.60 (m, 2H), 7.13-7.11 (m, 1H), 7.21 (t, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 1.8 Hz, 1H), 7.43 (ddd, *J* = 7.9, 1.9, 1.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.31, 200.45, 138.49, 131.80, 131.06, 130.84, 126.61, 123.31, 77.73, 70.34, 42.30, 30.51, 29.81.

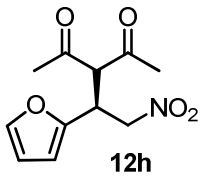


12g

(*R*)-3-(1-(2,4-dichlorophenyl)-2-nitroethyl)pentane-2,4-dione (12g) [5] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 91% yield. HPLC with Chiralcel AD-H column (Hexanes:isopropanol, (90:10), 1.0 ml/min, 230 nm) t_{minor} = 10.1 min, t_{major} = 12.6 min, 93 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.06 (s, 3H), 2.29 (s, 3H), 4.54 (d, *J* = 9.8 Hz, 1H), 4.62 (dd, *J* = 12.4, 4.0 Hz, 1H), 4.71-4.67 (m, 1H), 4.82 (dd, *J* = 12.5, 6.8 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.57, 200.52, 135.09, 134.52, 132.13, 130.48, 129.91, 127.99, 75.97, 68.81, 38.43, 30.88, 28.62.

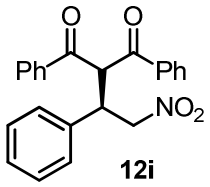


12h

(*S*)-3-(1-(furan-2-yl)-2-nitroethyl)pentane-2,4-dione (12h) [5] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as yellow solid 91% yield. HPLC with Chiralcel AD-H column (Hexanes:isopropanol, (90:10), 0.8ml/min, 210 nm) t_{minor} = 21.7 min, t_{major} = 26.3 min, 94 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.08 (s, 3H), 2.28 (s, 3H), 4.40-4.33 (m, 2H), 4.66 (d, *J* = 5.5 Hz, 2H), 6.18 (d, *J* = 3.2 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.8 Hz, 1H), 7.36 (dd, *J* = 1.8, 0.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.46, 200.77, 149.44, 142.90, 110.82, 108.85, 75.82, 67.90, 36.57, 30.63, 29.29.

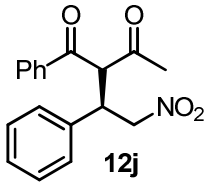


12i

(*R*)-2-(2-nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione (12i) [6] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 56 % yield. HPLC with Chiralcel AS-H column (Hexanes:isopropanol, (85:15), 1ml/min, 210 nm) t_{minor} = 25.6 min, t_{major} = 35.7 min, 86 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.63 (dd, *J* = 7.7, 14.7 Hz, 1H), 5.0-4.98 (m, 2H), 5.84 (d, *J* = 7.8 Hz, 1H), 7.24-7.15 (m, 5H), 7.40-7.32 (m, 3H), 7.55-7.47 (m, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.24, 193.63, 136.78, 136.20, 135.83, 134.07, 133.80, 129.53, 128.97, 128.96, 128.83, 128.78, 128.60, 128.26, 128.16, 77.35, 59.86, 44.04.



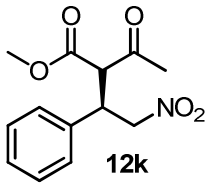
12j

(*S*)-2-((R)-2-nitro-1-phenylethyl)-1-phenylbutane-1,3-dione (12j) [7] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 88 % yield (1:1 mixture of diastereomers). HPLC with Chiralcel AD-H column (Hexanes:isopropanol, (98:2), 1ml/min, 215 nm) Major diastereomer : t_{minor}=34.2min, t_{major}=45.2 min, 92 %ee. Minor diastereomer: t_{major} = 39.8 min, t_{minor} = 55.8 min, 90 %ee.

Major diastereomer marked with asterisk.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.93 (s, 3H)*, 2.22 (s, 3H), 4.45-4.39 (m, 1H), 4.55-4.50 (m, 1H)*, 4.63-4.71 (m, 2H)*, 4.75 (dd, *J* = 13.2, 4.6 Hz, 1H), 4.85 (dd, *J* = 12.8, 8.6 Hz, 1H), 5.17 (d, *J* = 9.9 Hz, 1H)*, 5.19 (d, *J* = 9.1 Hz, 1H), 7.11-7.20 (m, 5H), 7.25-7.34 (m, 5H)*, 7.39-7.43 (m, 2H), 7.47-7.51 (m, 2H)*, 7.53-7.57 (m, 1H)*, 7.61-7.65 (m, 1H), 7.79-7.81 (m, 2H)*, 8.00-8.02 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.6, 200.7*, 194.1*, 193.7, 136.5, 136.3, 136.2*, 136.0*, 134.5*, 134.1, 129.3*, 129.1*, 129.0, 128.9*, 128.5, 128.2*, 128.1, 128.0, 78.2*, 78.1, 65.4*, 64.8, 43.4, 43.3*, 29.8, 28.5*

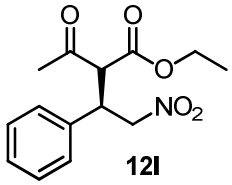


12k

(2*S*,3*R*)-methyl 2-acetyl-4-nitro-3-phenylbutanoate (12k) [8] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 98 % yield (1:1 mixture of diastereomers). HPLC with Chiralcel OD-H column (Hexanes:isopropanol, (98:2), 1ml/min, 230 nm) Major diastereomer : t_{major} = 22.8 min, t_{minor} = 23.9 min, 89 %ee. Minor diastereomer: t_{major} = 29.3 min, t_{minor} = 33.5 min, 89 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.05 (s, 1.1 H), 2.29 (s, 1.78 H), 3.53 (s, 1.78 H), 3.78 (s, 1.12 H), 4.06 (d, *J* = 9.7 Hz, 0.4 H), 4.14 (d, *J* = 9.6 Hz, 0.6 H), 4.27-4.21 (m, 1H), 4.78 (d, *J* = 5.5 Hz, 1.2 H), 4.87-4.82 (m, 0.7H), 7.22-7.19 (m, 2H), 7.32-7.28 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.14, 200.30, 168.02, 167.56, 167.40, 136.44, 136.30, 129.18, 129.13, 129.00, 128.40, 128.30, 127.89, 127.85, 77.77, 76.76, 61.82, 61.42, 52.97, 52.76, 52.33, 49.81, 42.61, 42.31, 30.38, 30.25, 30.14.

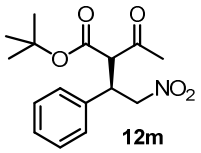


12l

(2*R*,3*R*)-ethyl 2-acetyl-4-nitro-3-phenylbutanoate (12l) [7] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 85 % yield (1:1 mixture of diastereomers). HPLC with Chiralcel AD-H column (hexanes:isopropanol, (95:5), 0.8 ml/min, 215 nm) Major diastereomer : t_{minor} = 16.03 min, t_{major} = 23.6 min, 93 %ee. Minor diastereomer: t_{major} = 25.7 min, t_{minor} = 46.4 min, 92 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.01-0.97 (m, 3H), 2.29 (s, 3H), 3.95 (q, *J* = 7.2 Hz, 2H), 4.12-4.10 (m, 1H), 4.23-4.17 (m, 1H), 4.75-4.74 (m, 2H), 7.21-7.18 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.15, 167.53, 166.87, 136.46, 129.15, 128.94, 128.36, 128.27, 127.99, 127.90, 77.89, 77.79, 62.21, 62.00, 61.95, 61.68, 42.56, 42.32, 30.28, 30.08, 13.67.

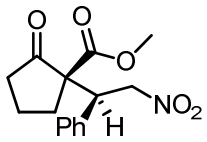


12m

(2*S*,3*R*)-tert-butyl 2-acetyl-4-nitro-3-phenylbutanoate (12m) [8] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 60 % yield (2.2:1 mixture of diastereomers). HPLC with Chiralcel AD-H column (hexanes:isopropanol, (95:5), 1.0 ml/min, 215 nm) Major diastereomer : t_{minor} = 9.1 min, t_{major} = 13.2 min, 89 %ee. Minor diastereomer: t_{major} = 16.8 min, t_{minor} = 22.9, 91 min, %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 5.8H), 1.46 (s, 2.5H), 2.05 (s, 0.8H), 2.30 (s, 1.8H), 3.92 (d, *J* = 9.6 Hz, 0.3H), 4.01 (d, *J* = 10.4 Hz, 0.6H), 4.21-4.10 (m, 1H), 4.75-4.65 (m, 1.3H), 4.88-4.78 (m, 0.5H), 7.22-7.19 (m, 2H), 7.33-7.25 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.36, 200.63, 165.86, 136.63, 129.08, 128.84, 128.25, 128.20, 127.97, 83.47, 82.93, 78.36, 77.87, 63.05, 62.72, 42.54, 42.35, 30.09, 29.69, 27.82, 27.35.

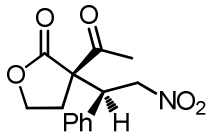


12n

(*R*)-methyl 1-((S)-2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate (12n) [9] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 89 % yield (2.2:1 mixture of diastereomers). HPLC with Chiralcel AD-H column (hexanes:isopropanol, (95:5), 1.0 ml/min, 215 nm) Major diastereomer : t_{minor} = 9.1 min, t_{major} = 13.2 min, 89 %ee. Minor diastereomer: t_{major} = 16.8 min, t_{minor} = 22.9 min, 91 %ee.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.04-1.80 (m, 4H), 2.40-2.31 (m, 2H), 3.75 (s, 3H), 4.07 (dd, *J* = 10.8, 3.8 Hz, 1H), 5.01 (dd, *J* = 13.7, 10.8 Hz, 1H), 5.16 (dd, *J* = 13.6, 3.9 Hz, 1H), 7.32-7.23 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 212.23, 169.81, 135.27, 129.30, 128.84, 128.33, 76.42, 62.45, 53.02, 46.18, 37.92, 31.13, 19.32.



(*S*)-3-acetyl-3-((S)-2-nitro-1-phenylethyl)dihydrofuran-2(3H)-one (12o) [5] The title compound was prepared according to the general procedure and purified by column chromatography, obtained as white solid 62 % yield (3:1 mixture of diastereomers). HPLC with Chiralcel OD-H column (hexanes:ethanol, (80:20), 1.0 ml/min, 210 nm) Major diastereomer : t_{minor} = 15.5 min, t_{major} = 41.0 min, 83 %ee. Minor diastereomer: t_{minor} = 10.8 min, t_{major} = 18.1 min, 88 %ee.

Major diastereomer ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.32-2.26 (m, 1H), 2.48 (s, 3H), 2.86-2.81 (m, 1H), 3.85 (td, *J* = 8.9, 4.2 Hz, 1H), 4.03 (q, *J* = 8.0 Hz, 1H), 4.56-4.49 (m, 2H), 4.85 (td, *J* = 13.2, 11.0 Hz, 1H), 7.36-7.34 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.23, 175.31, 133.10, 129.18, 129.13, 129.06, 74.97, 66.52, 64.67, 45.74, 26.22, 25.68.

Minor diastereomer ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.32-2.26 (m, 1H), 2.34 (s, 3H), 2.61-2.53 (m, 1H), 3.38-3.34 (m, 1H), 4.10-4.08 (m, 1H), 4.35 (dd, *J* = 11.1, 3.6 Hz, 1H), 4.74 (dd, *J* = 13.5, 3.5 Hz, 1H), 5.06 (dd, *J* = 13.4, 11.1 Hz, 1H), 7.36-7.34 (m, 5H),

^{13}C NMR (100 MHz, $CDCl_3$): δ 201.23, 173.12, 134.21, 129.43, 129.16, 128.67, 76.36, 67.08, 65.98, 46.26, 30.04, 26.56.

References:

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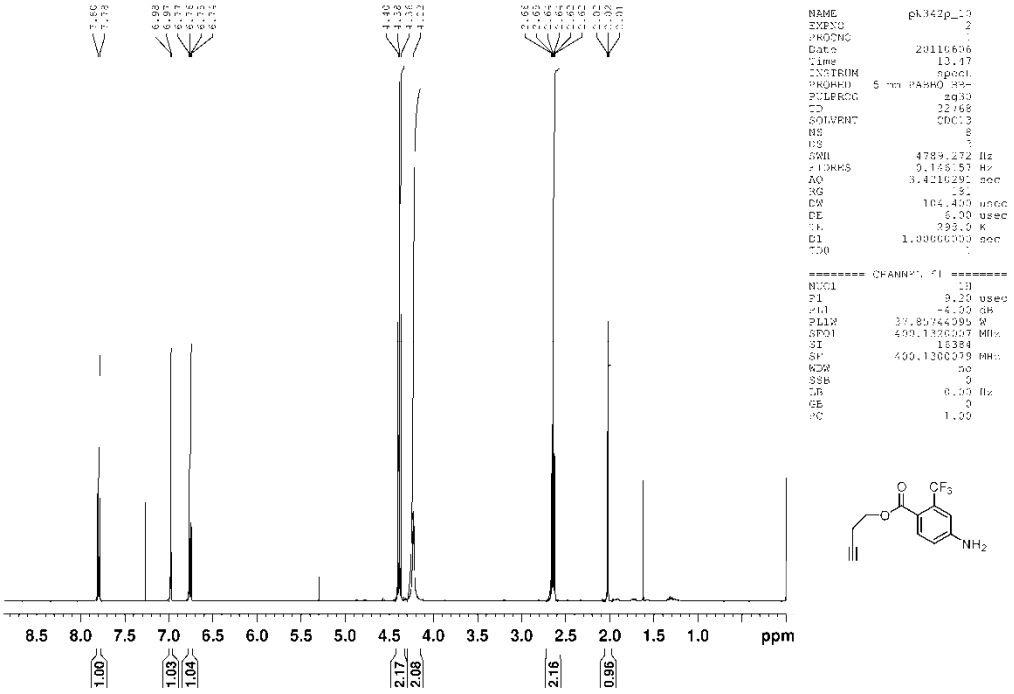
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2.65
2.64
2.63
2.62
2.61
2.60
2.59
2.02
2.01
2.00
1.99
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.03
1.04
2.17
2.08
2.16
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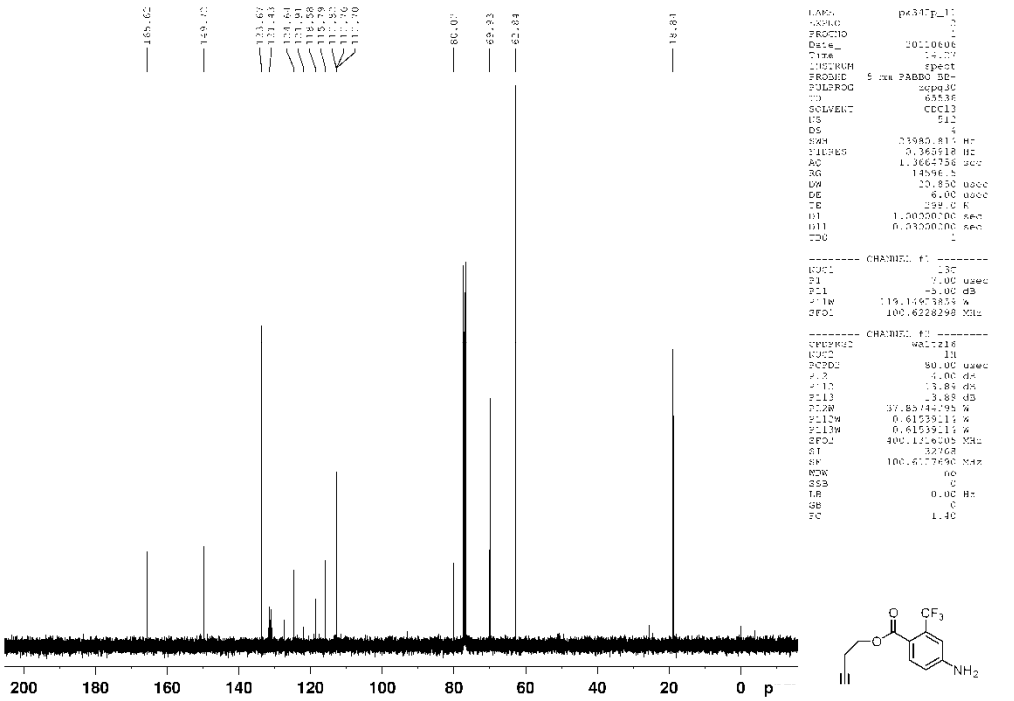
CF3
O
NH2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DE 6.00 usec
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D1 1.00000000 sec
D11 0.03000000 sec
TD0 1
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PL1 -3.00 dB
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SFO1 100.6228298 MHz
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PCPD2 80.00 usec
PL2 1.00 dB
PL12 13.84 dB
PL13 13.84 dB
PL2W 37.80744095 W
PL12W 0.61539111 W
PL13W 0.61539111 W
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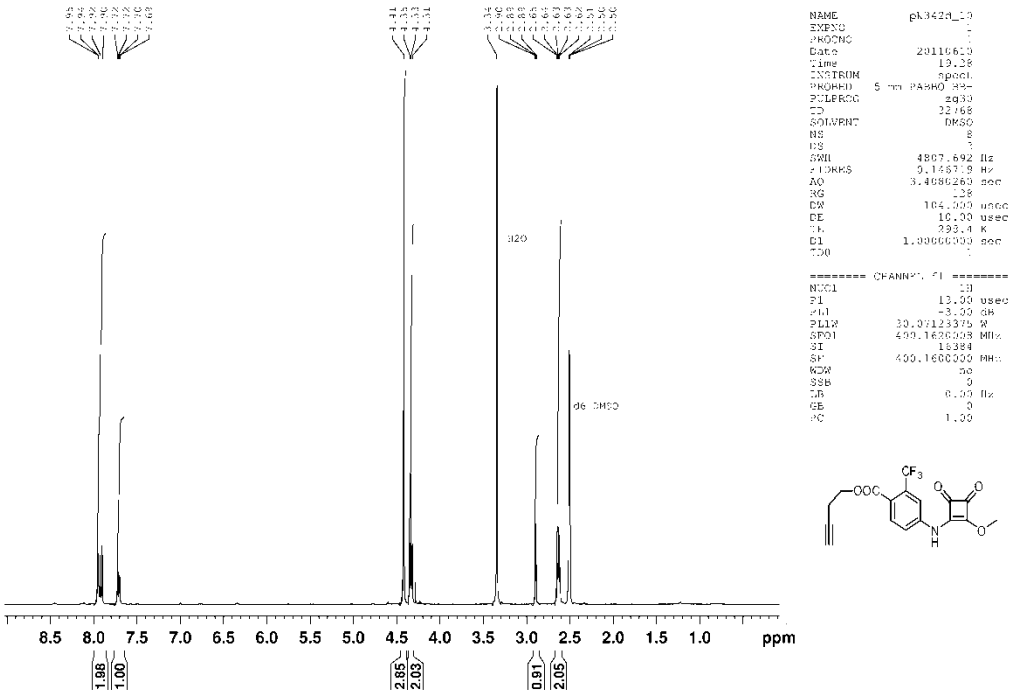

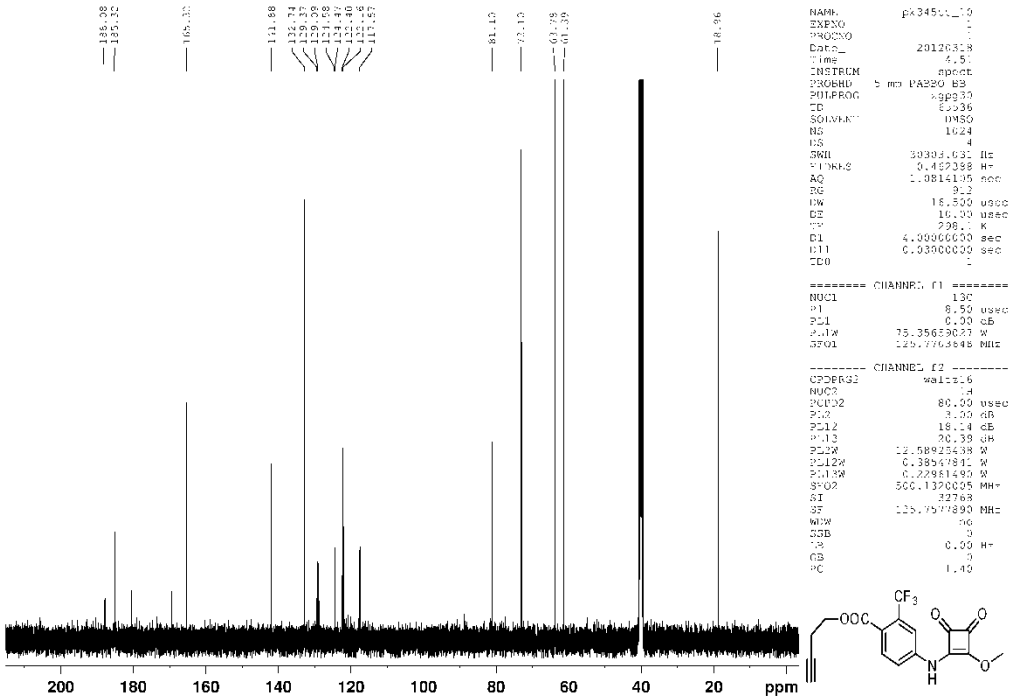

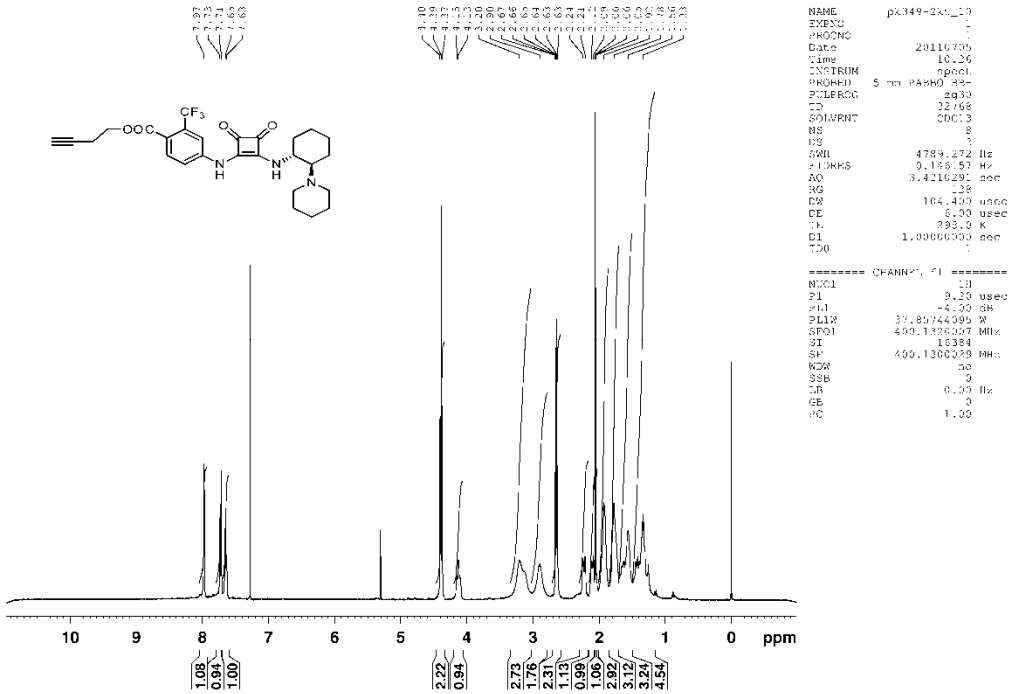

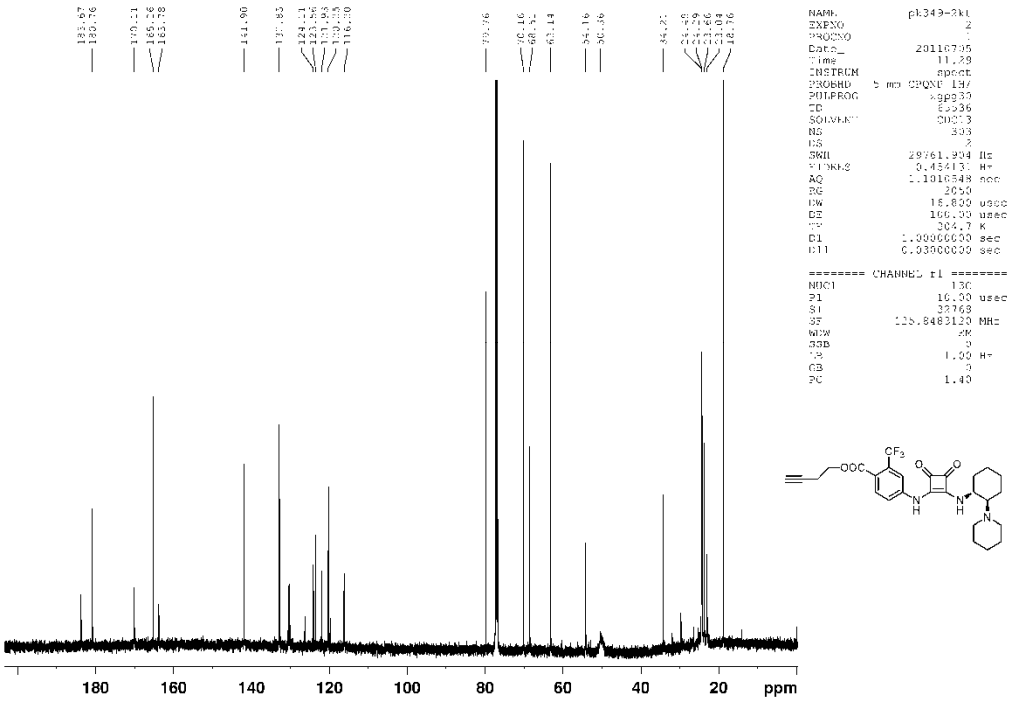

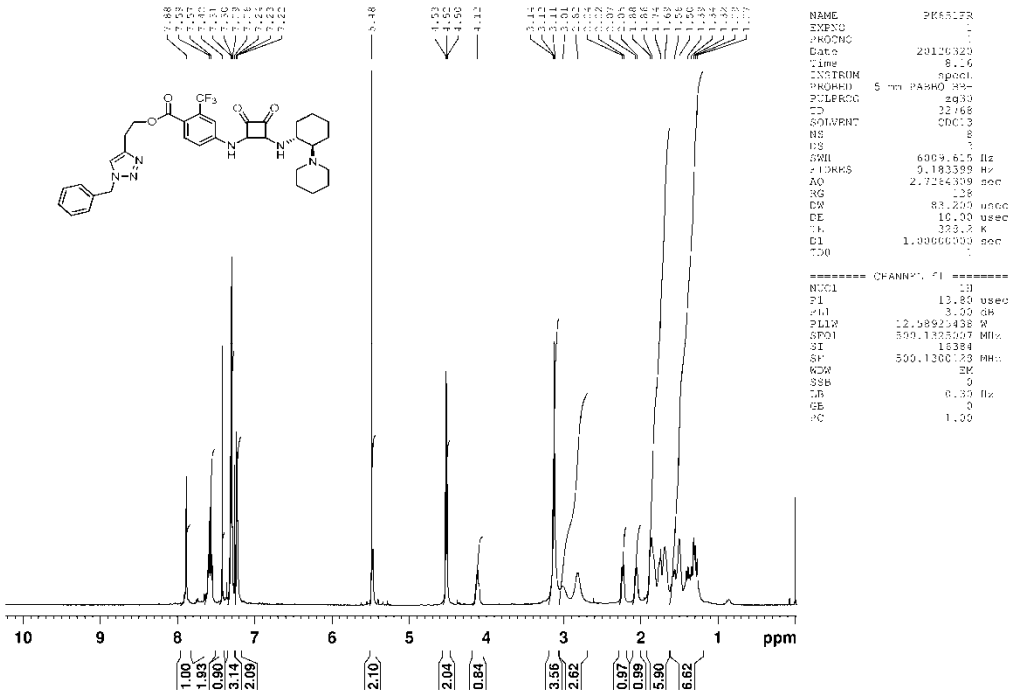

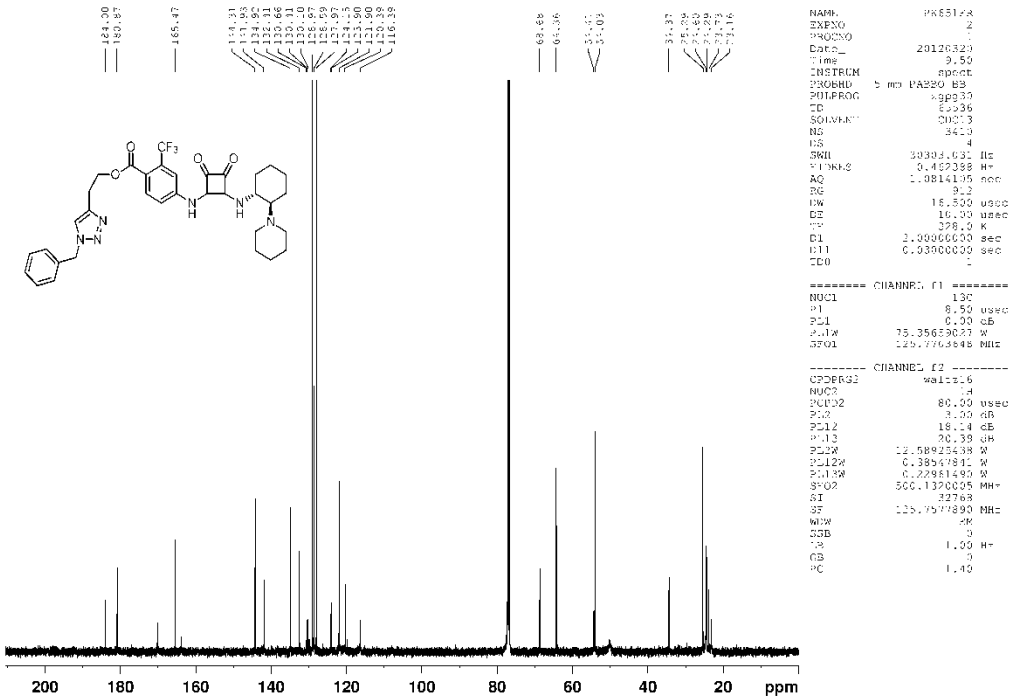

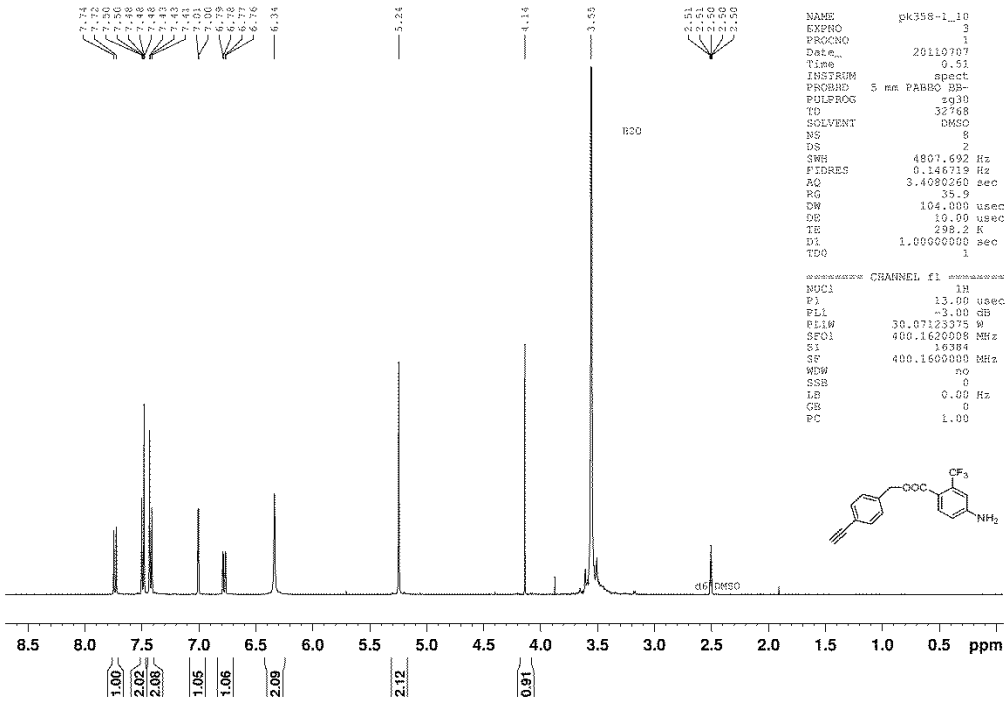

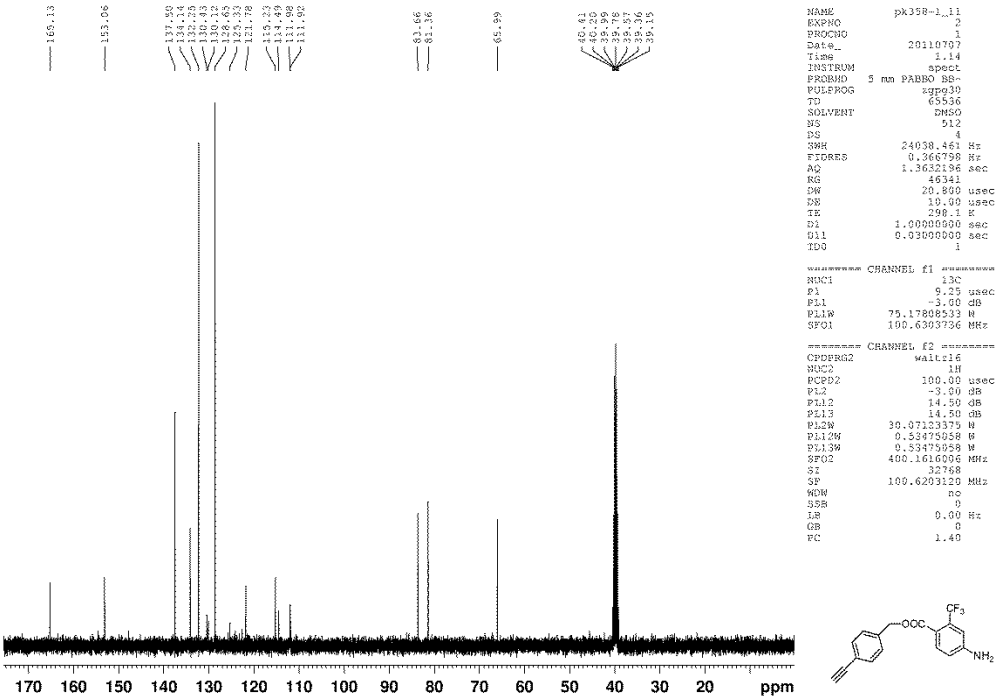

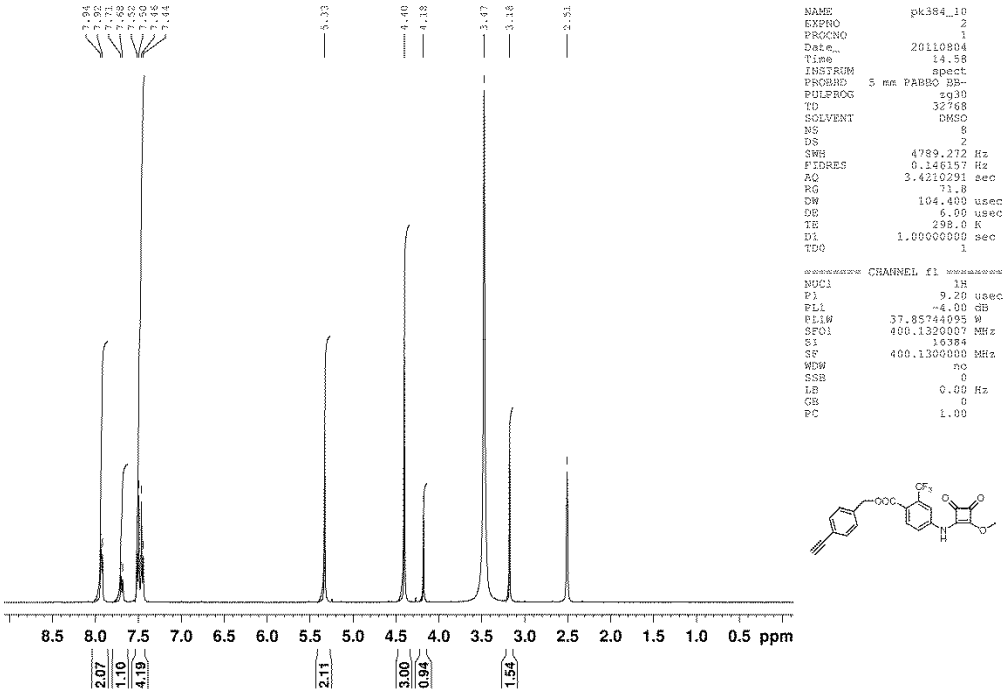

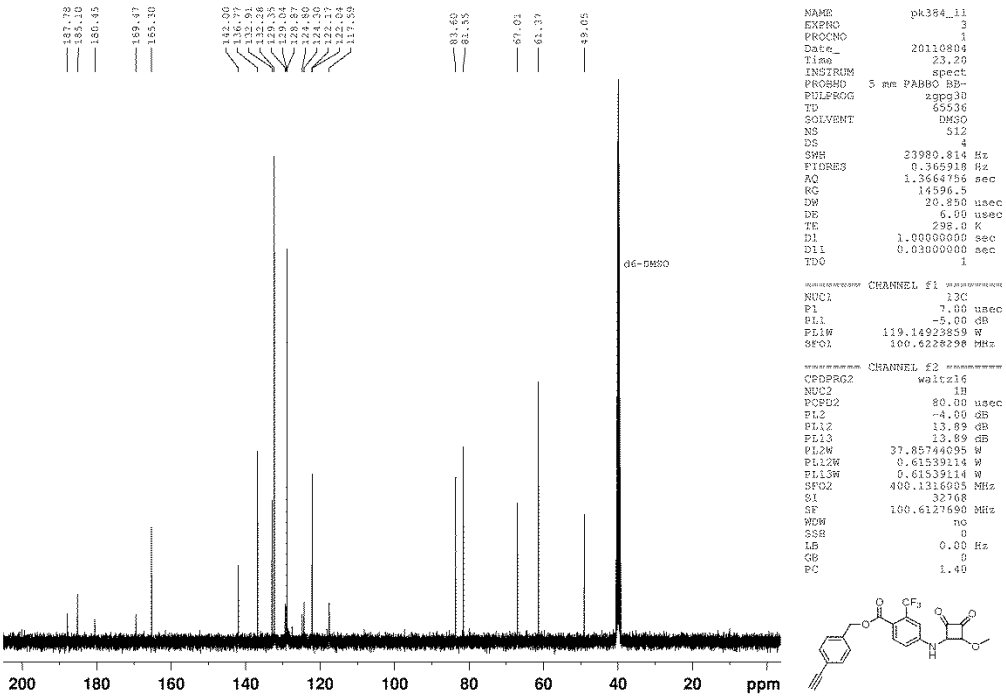

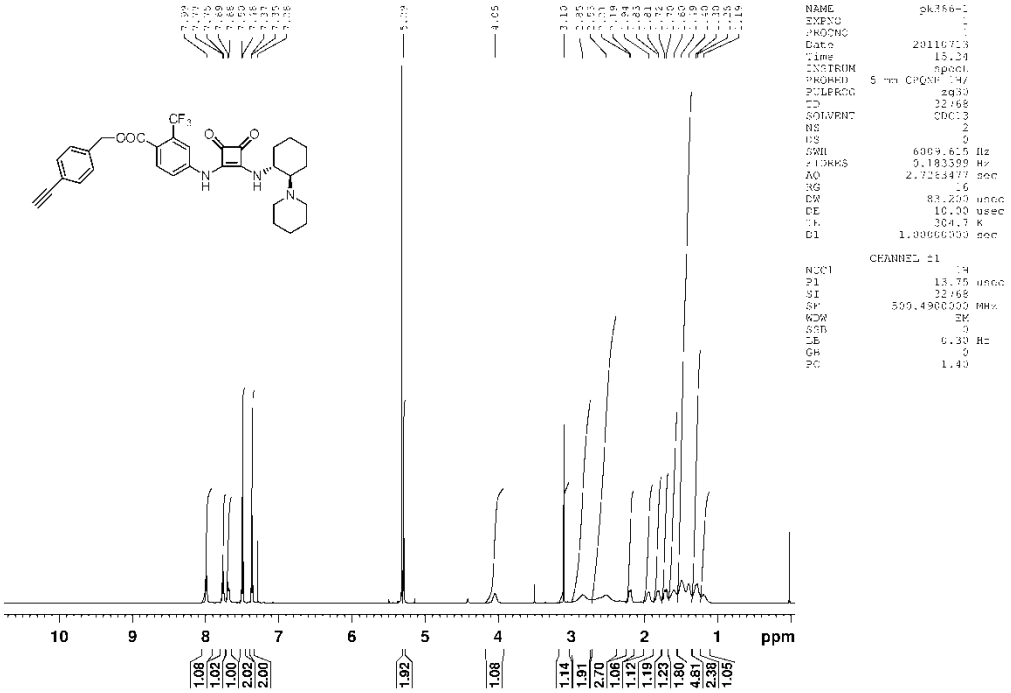

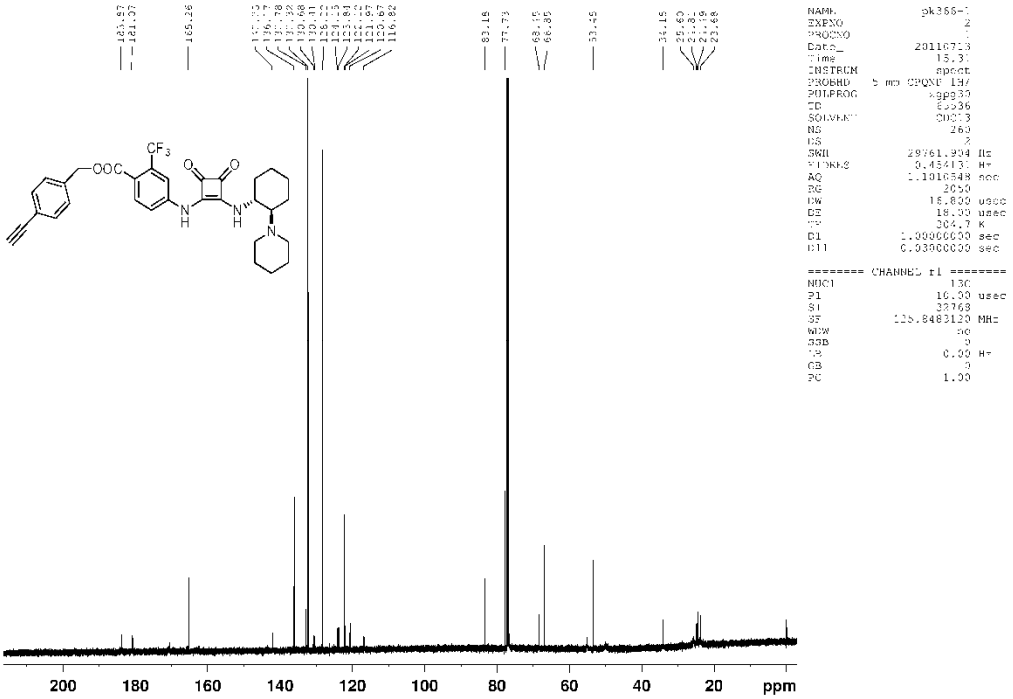

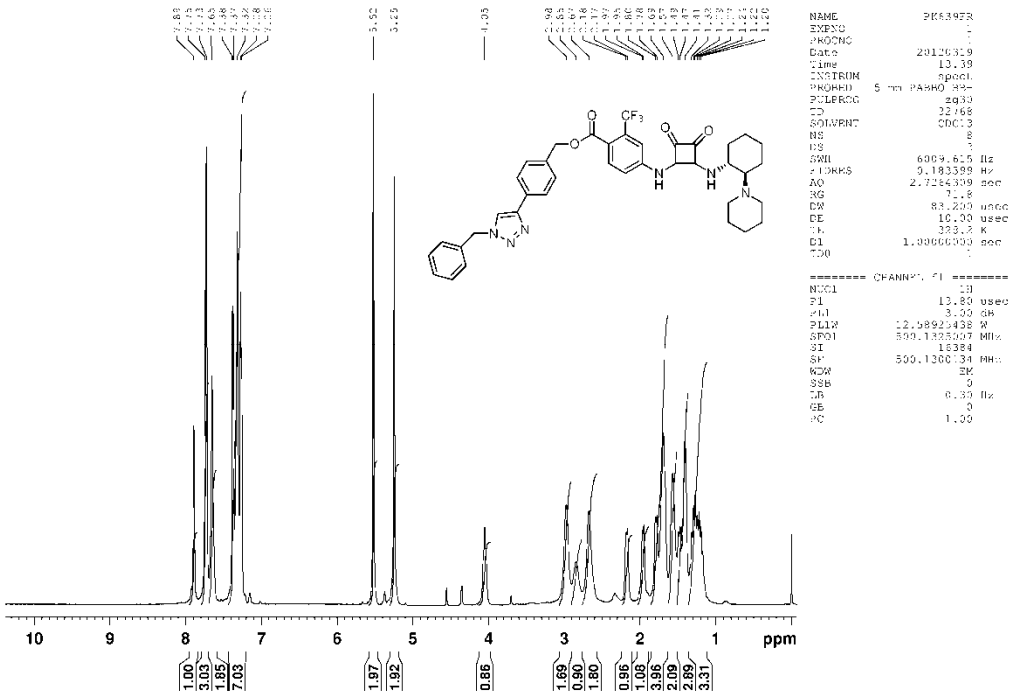

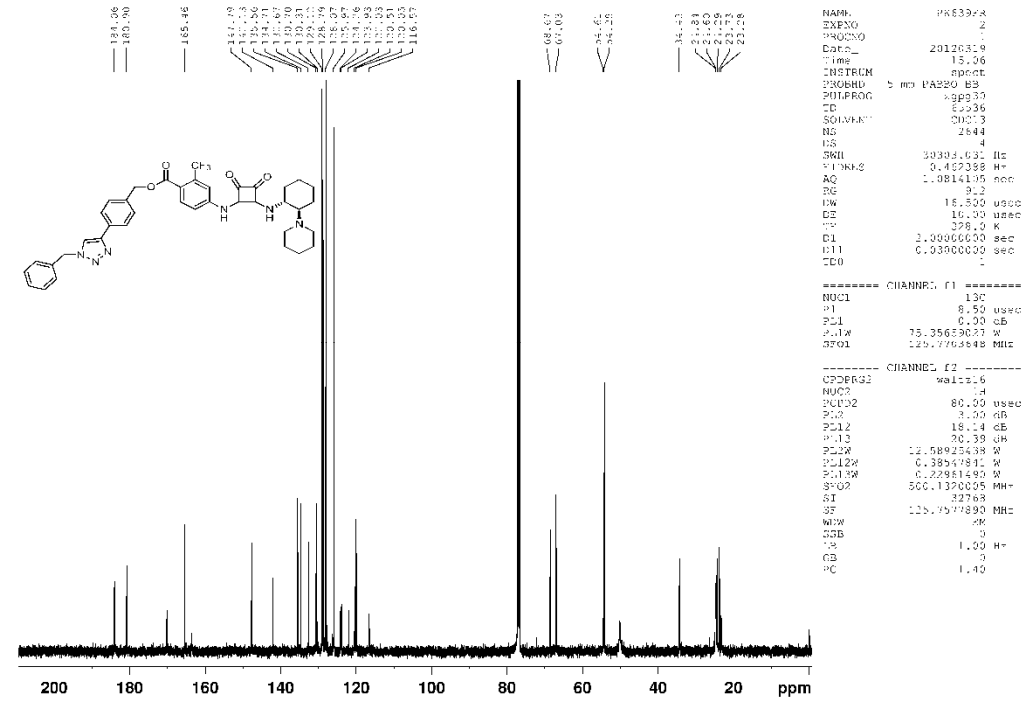

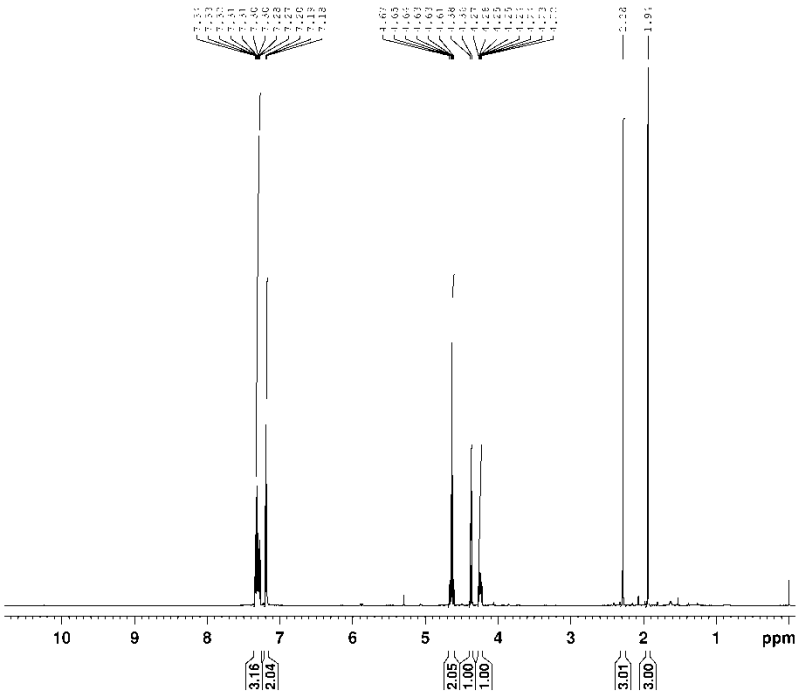


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D1               1.00000000 sec
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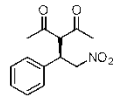

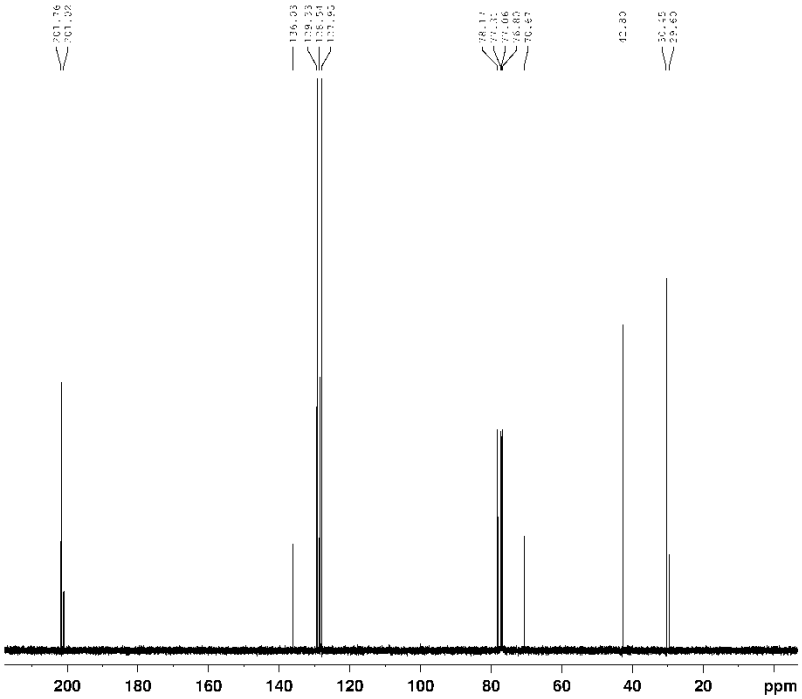


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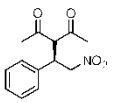

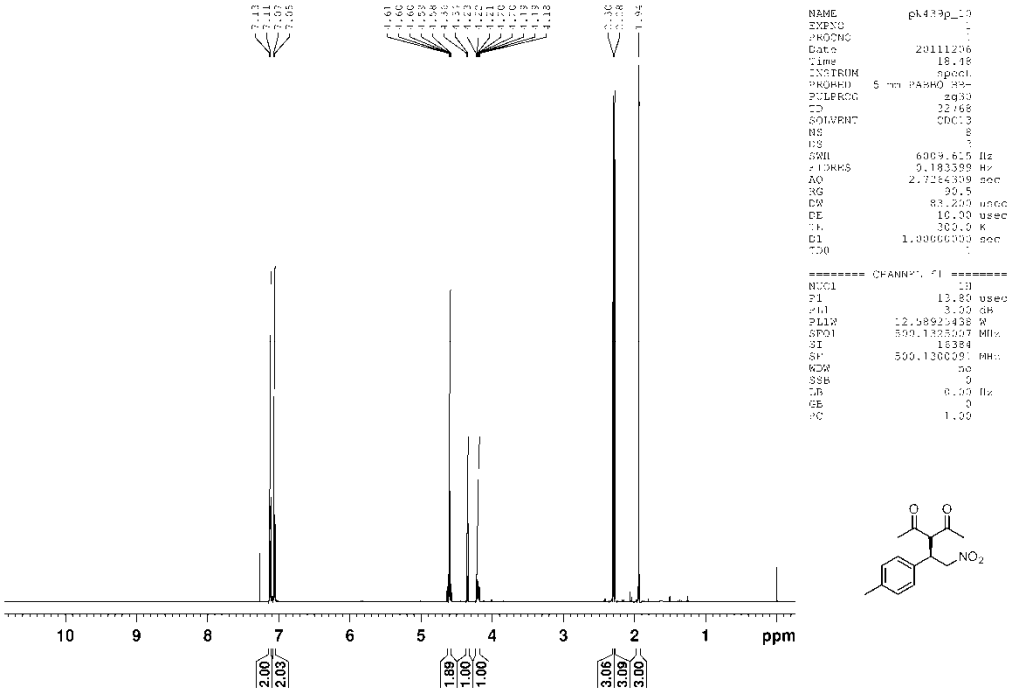

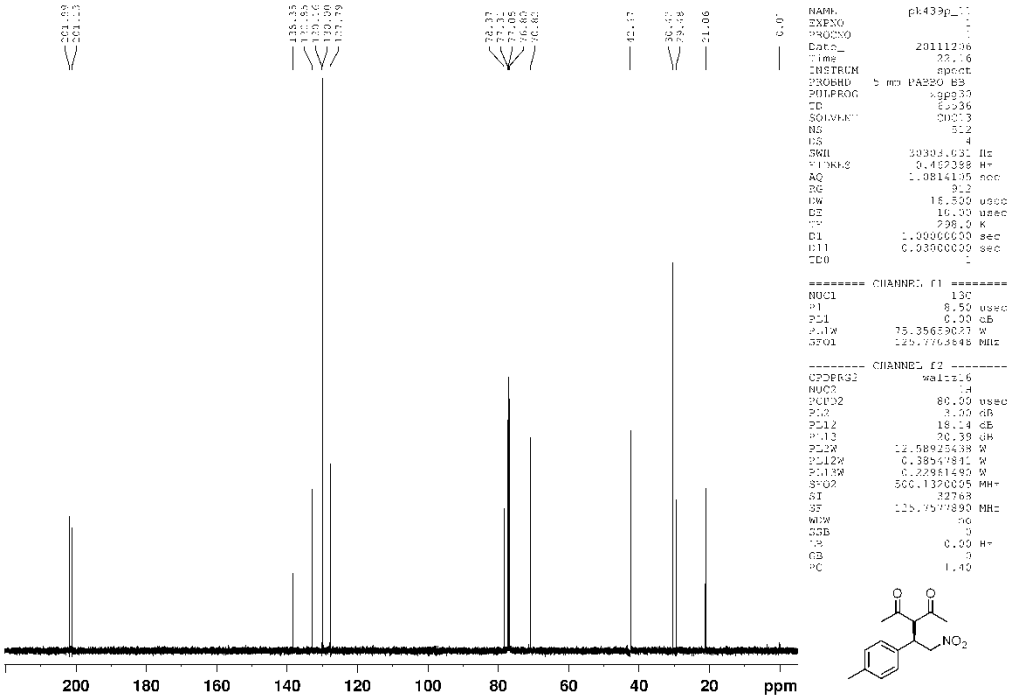

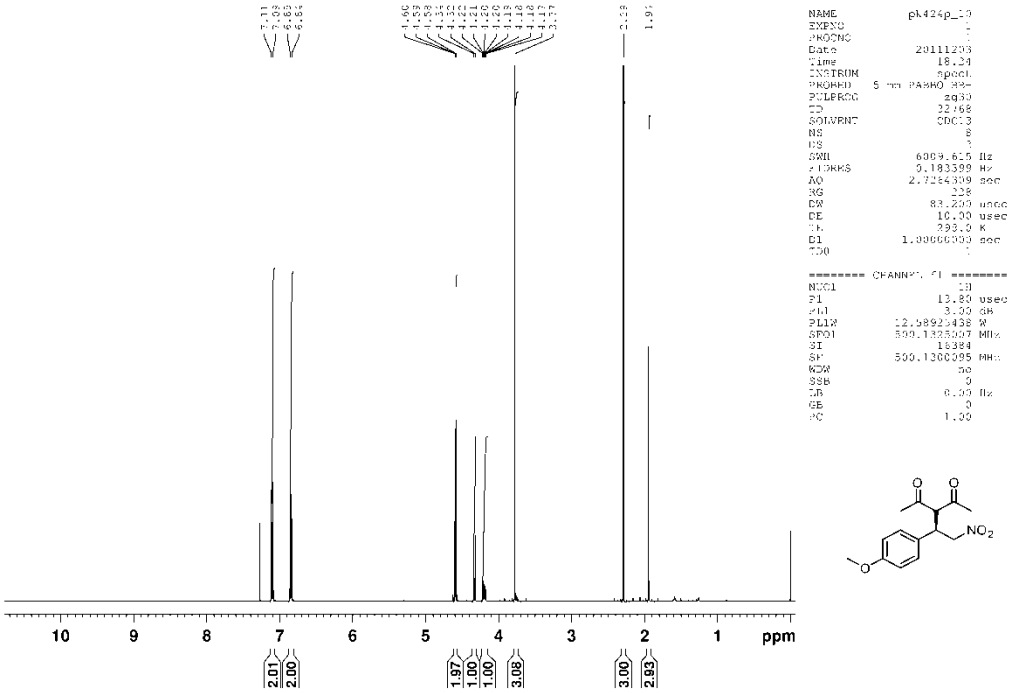
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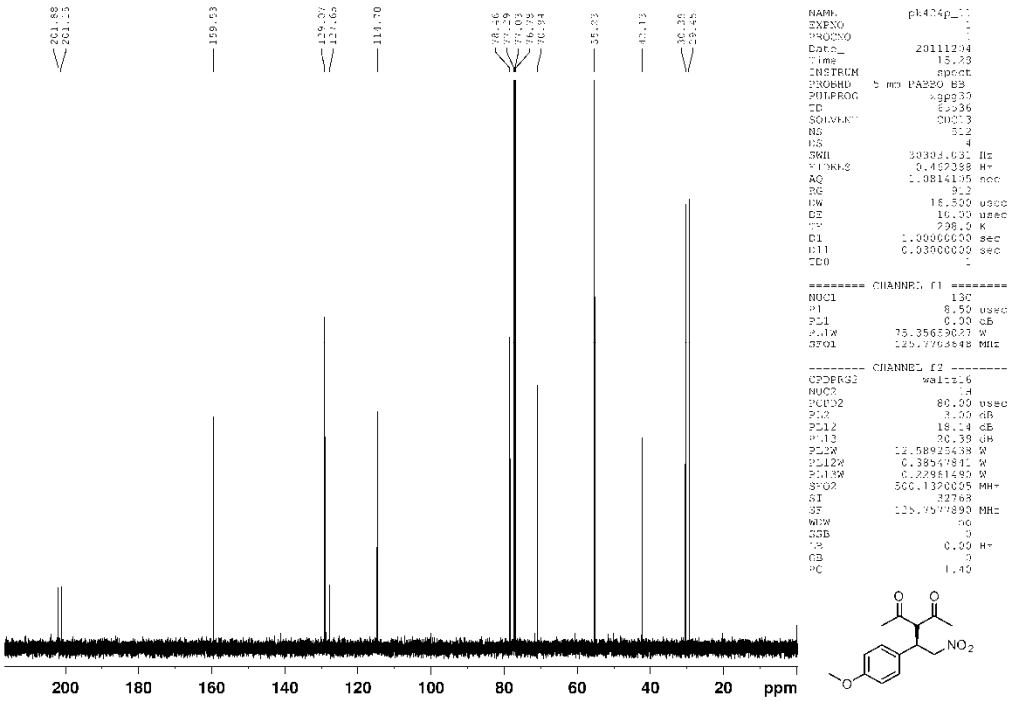
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PL13 20.39 dB
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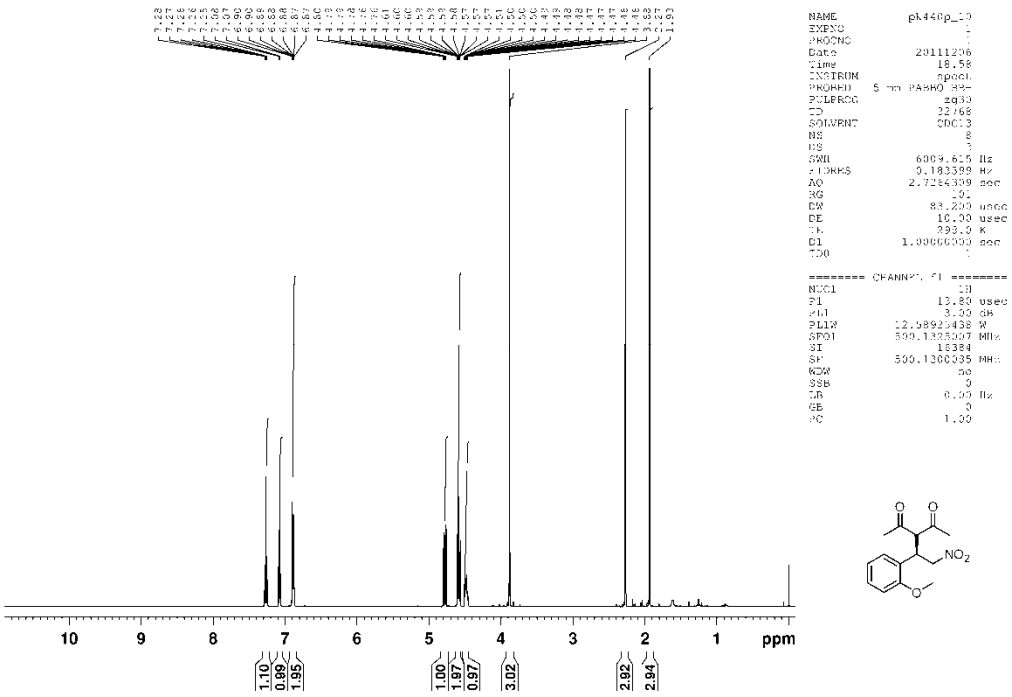

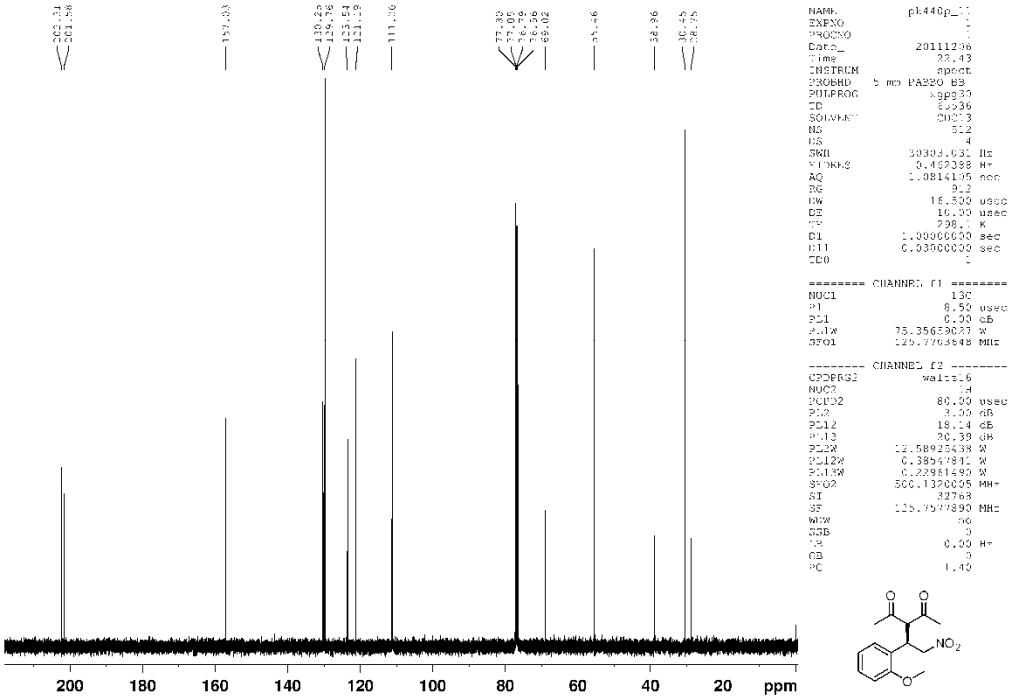

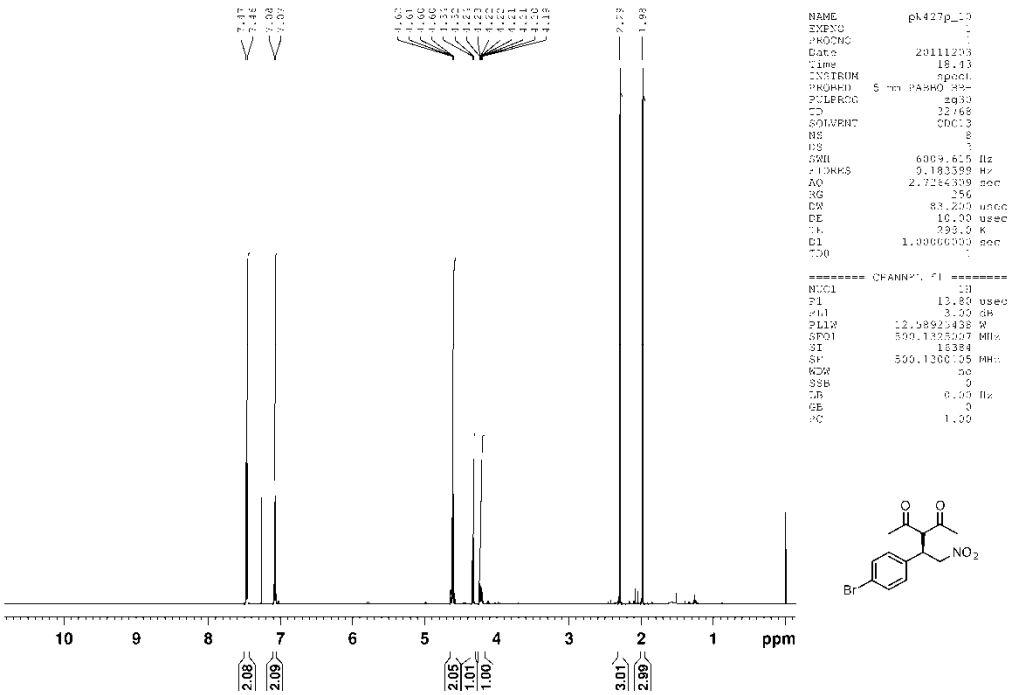

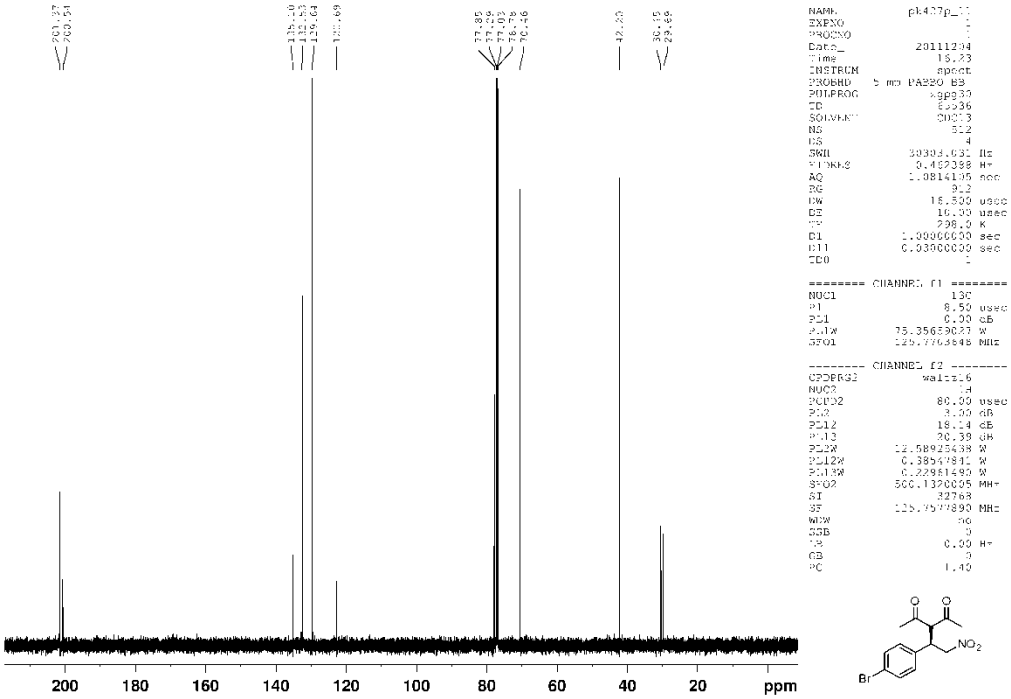

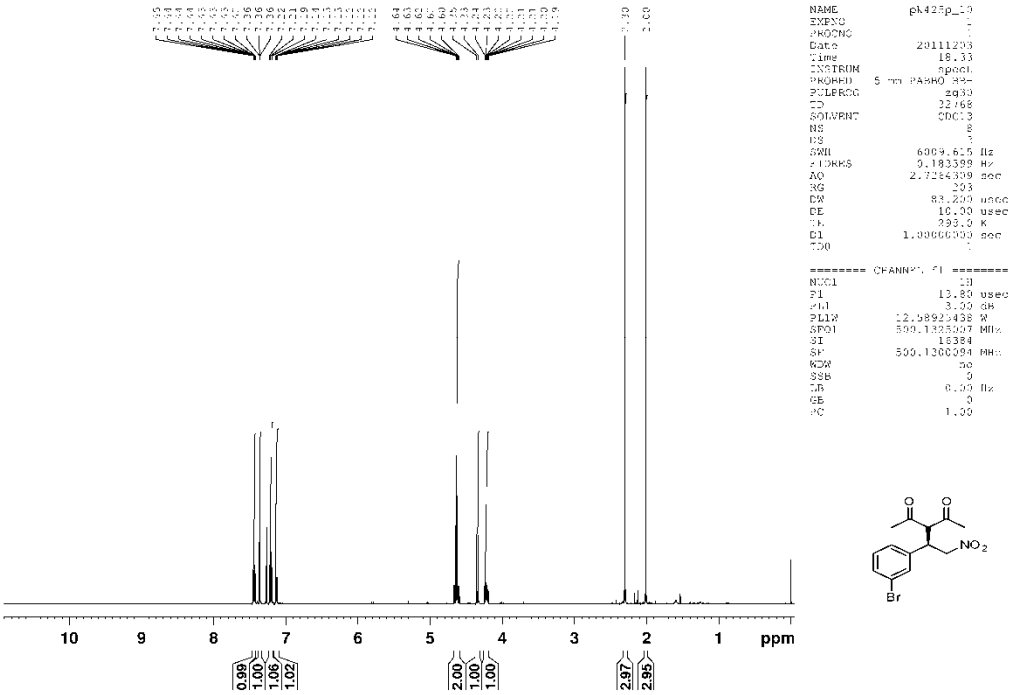

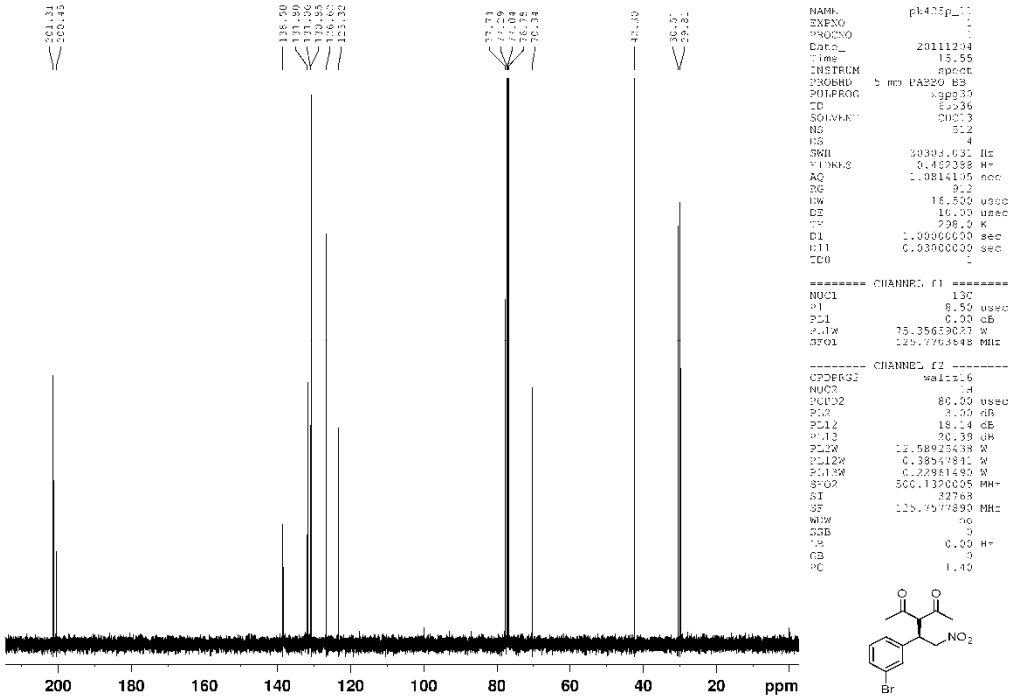

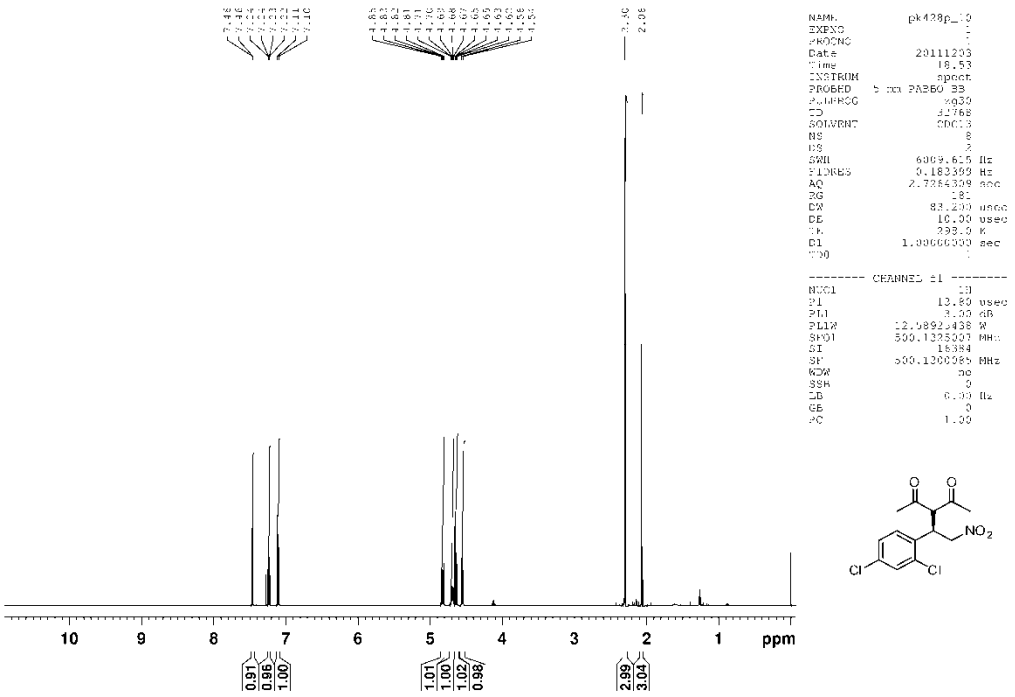

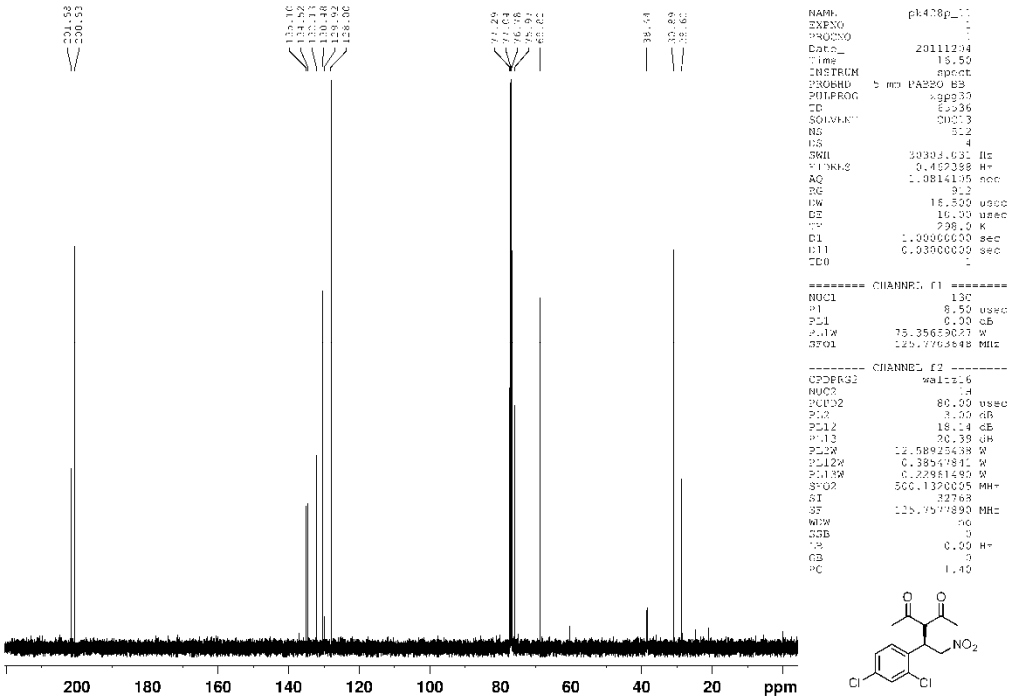

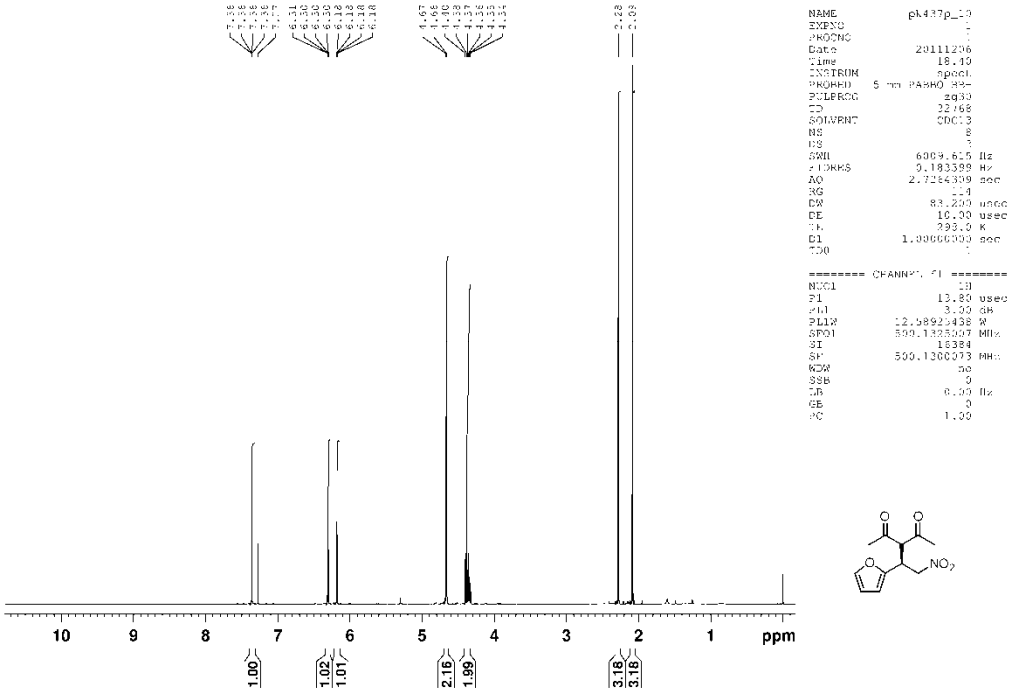

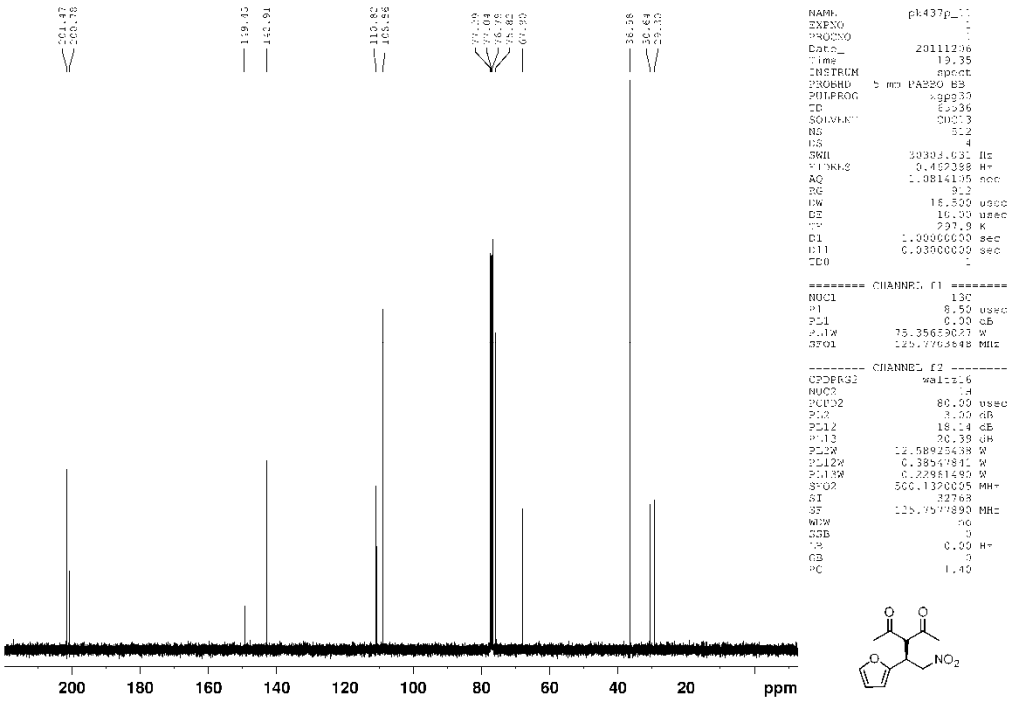

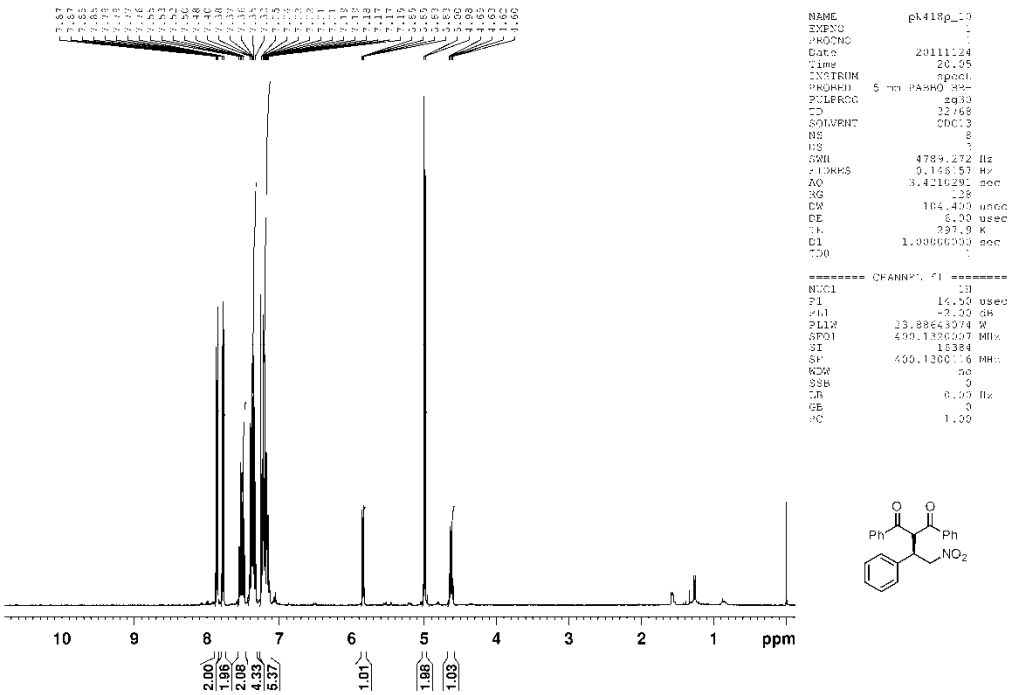

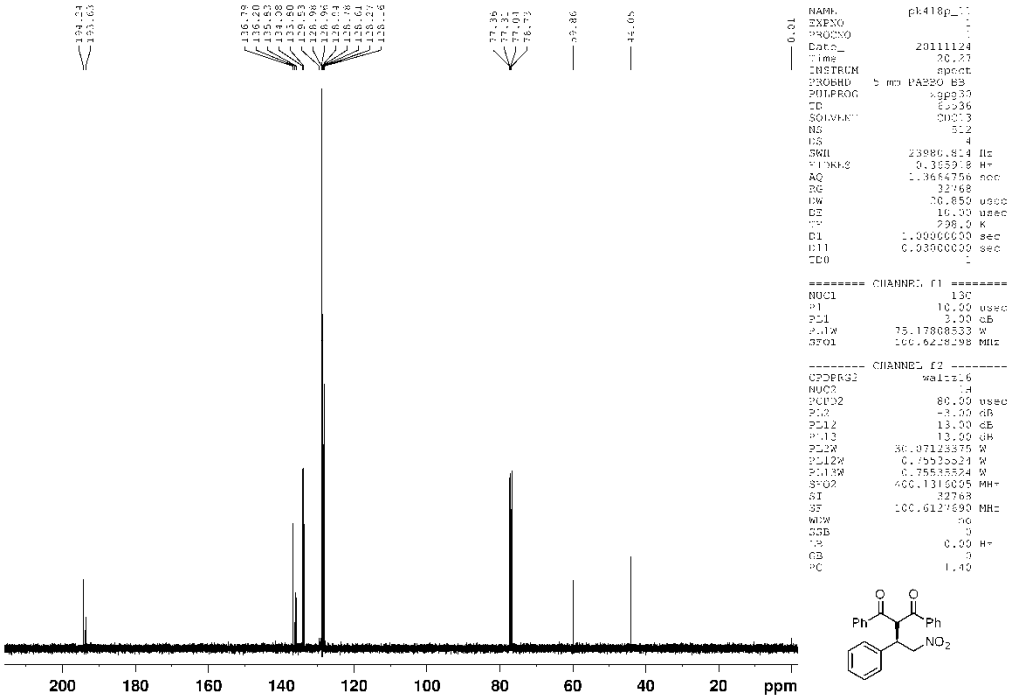

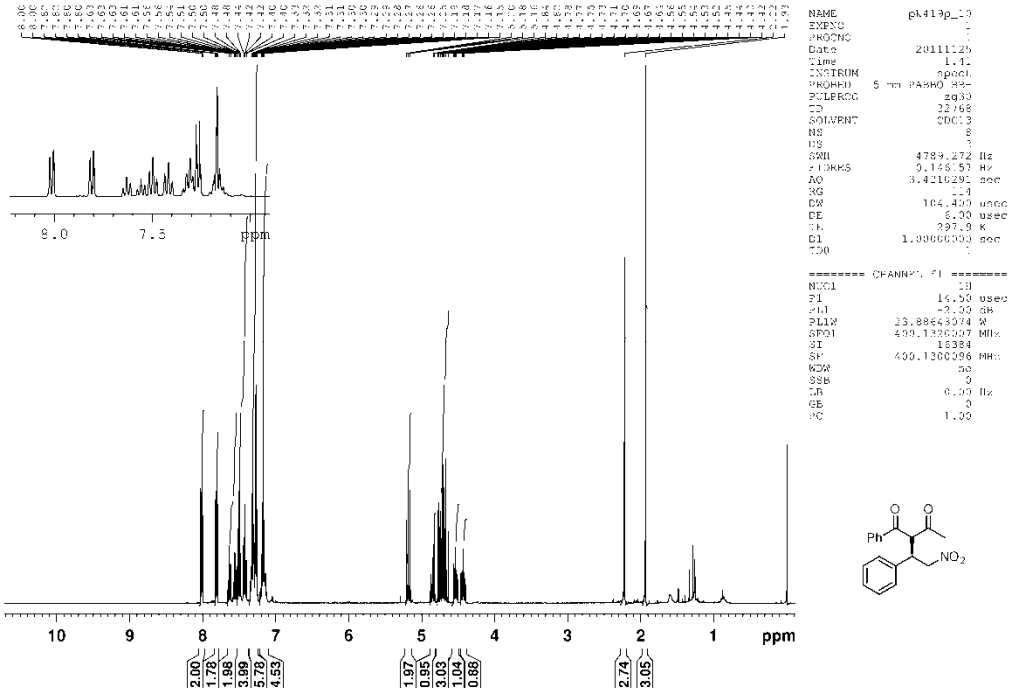

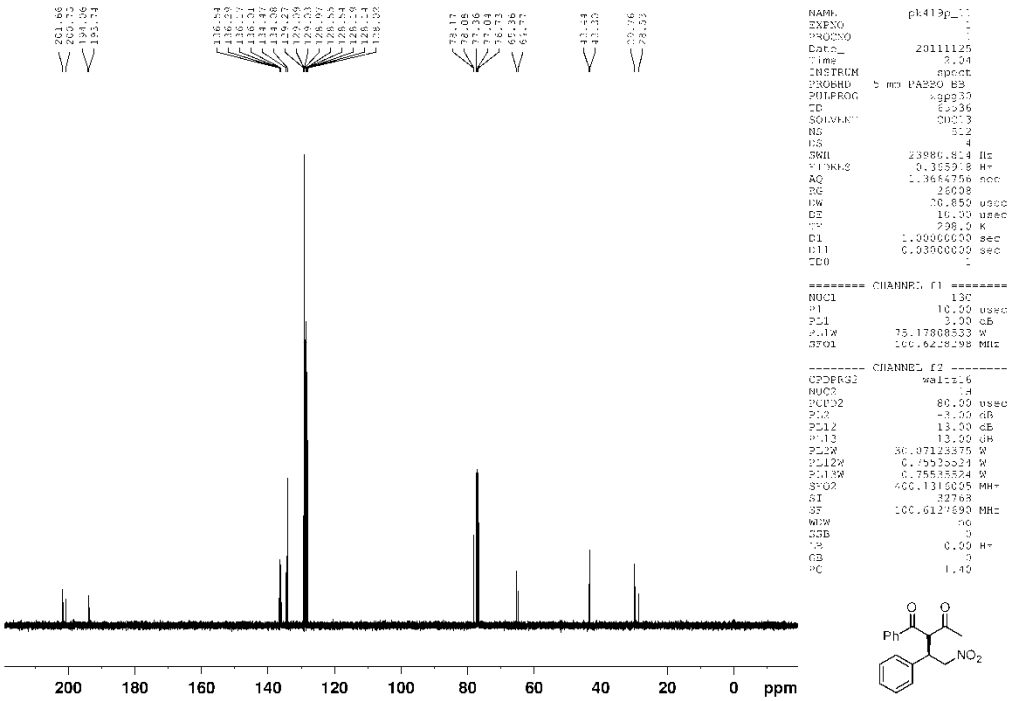

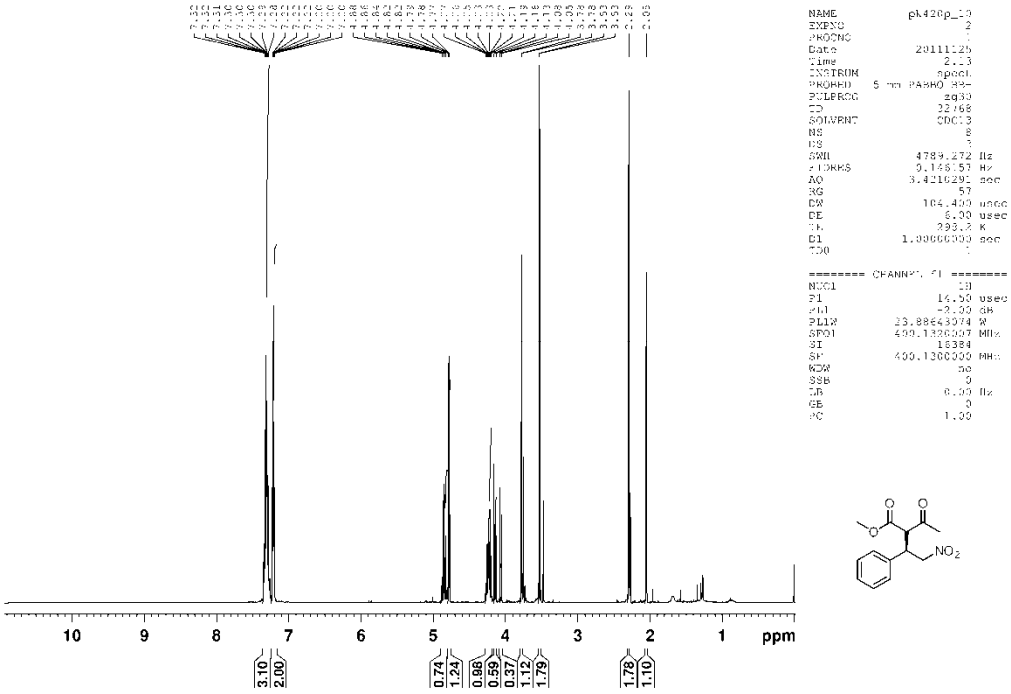

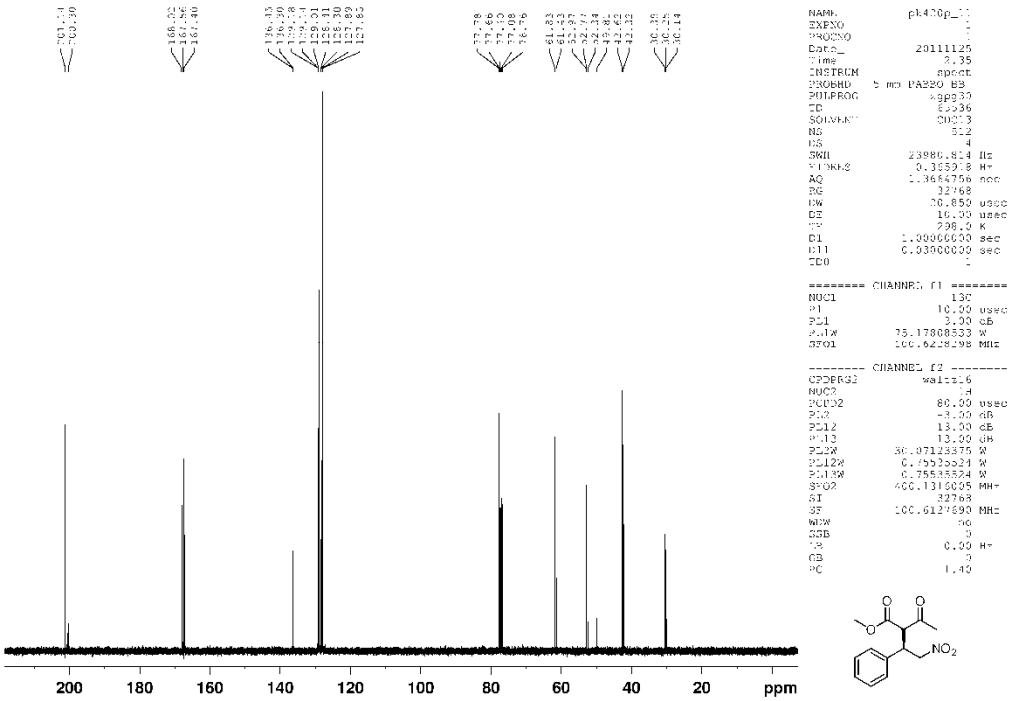

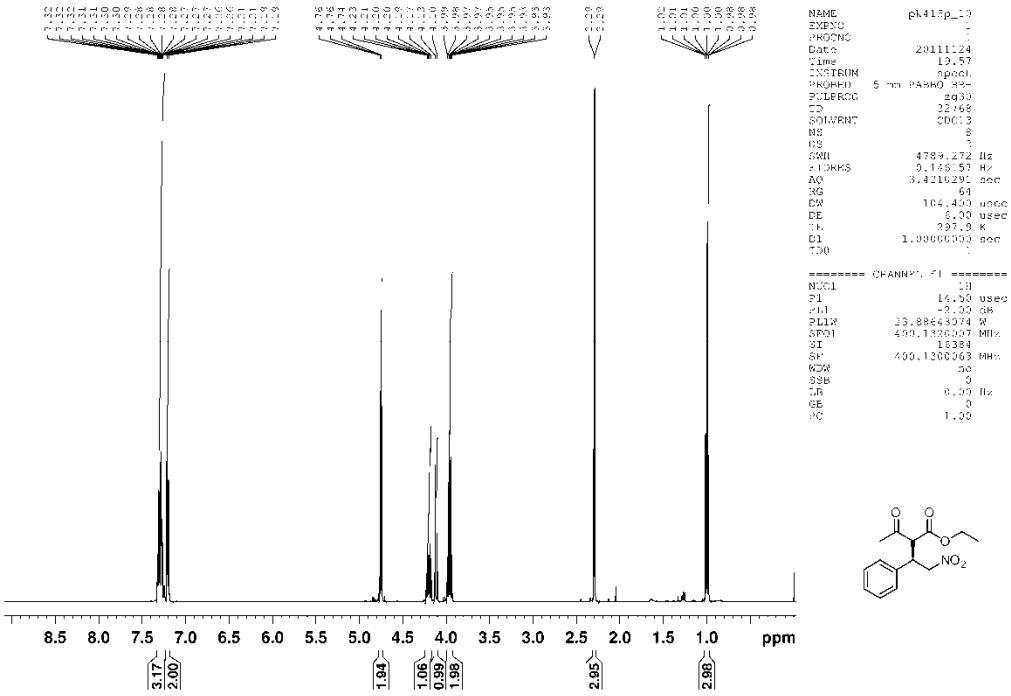

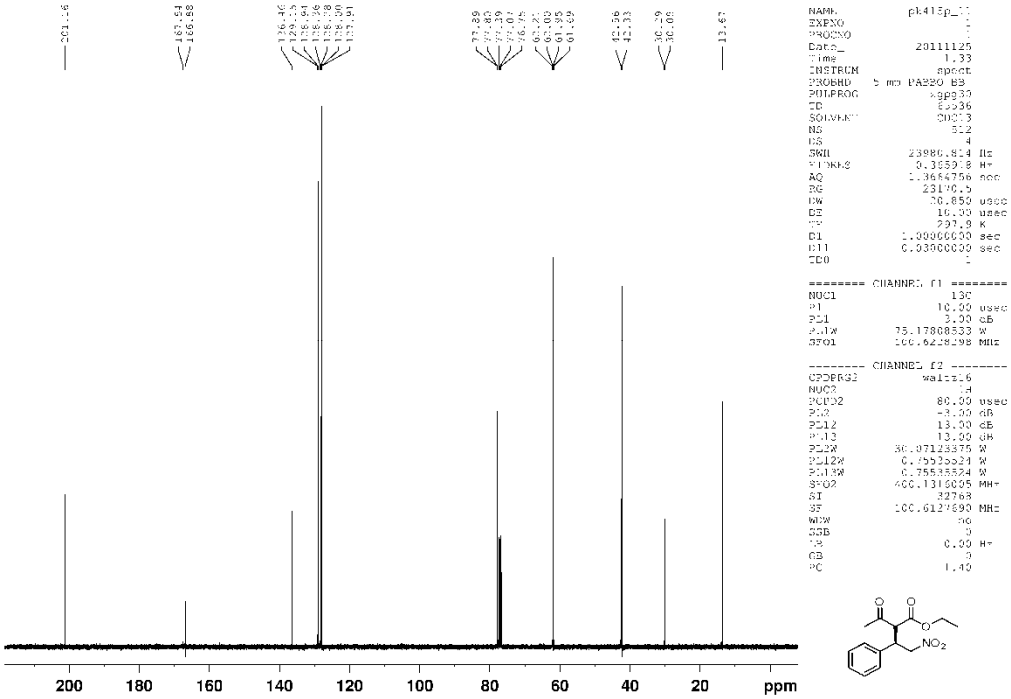

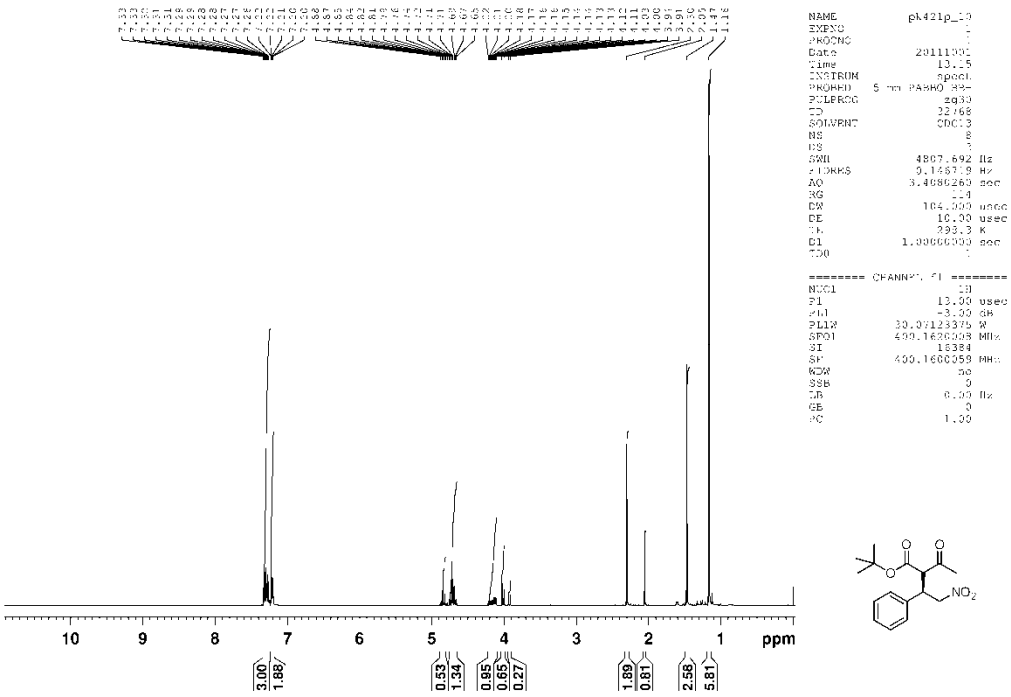

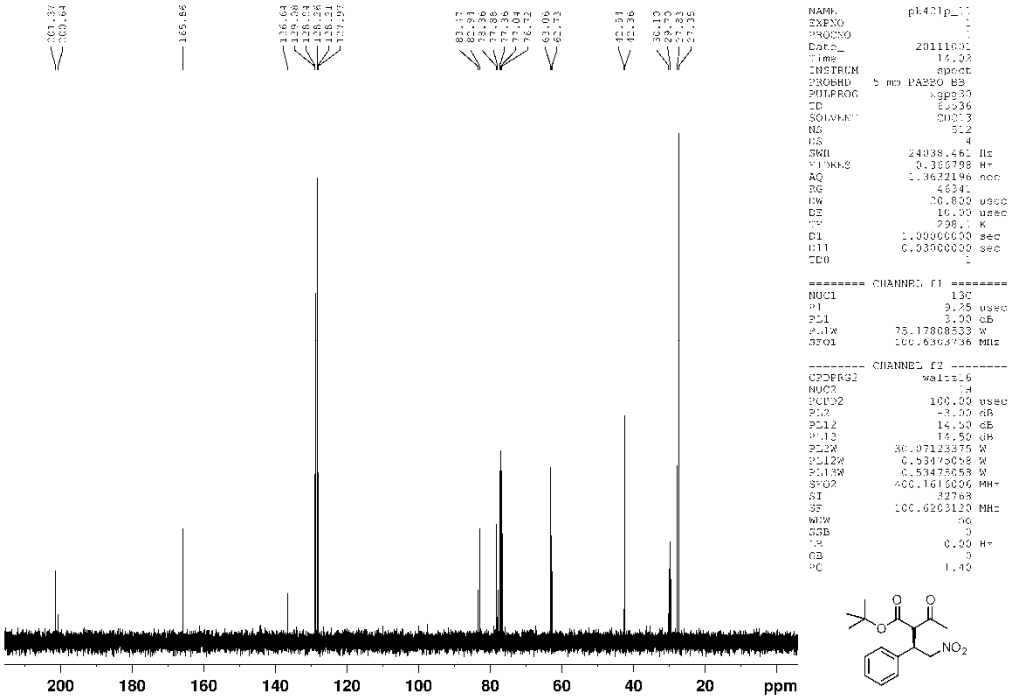

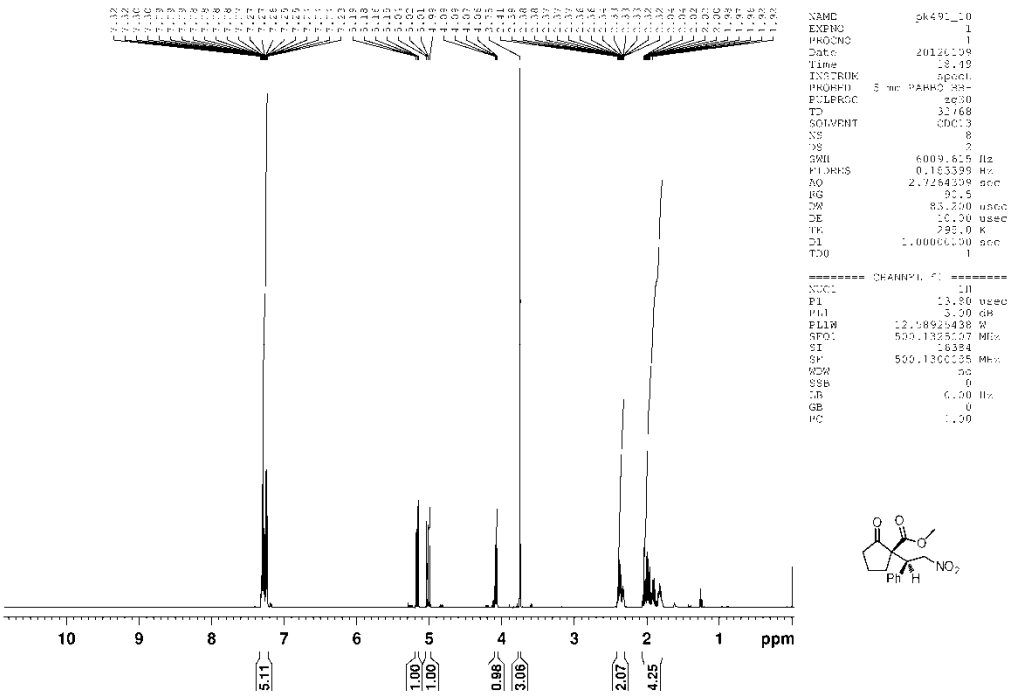

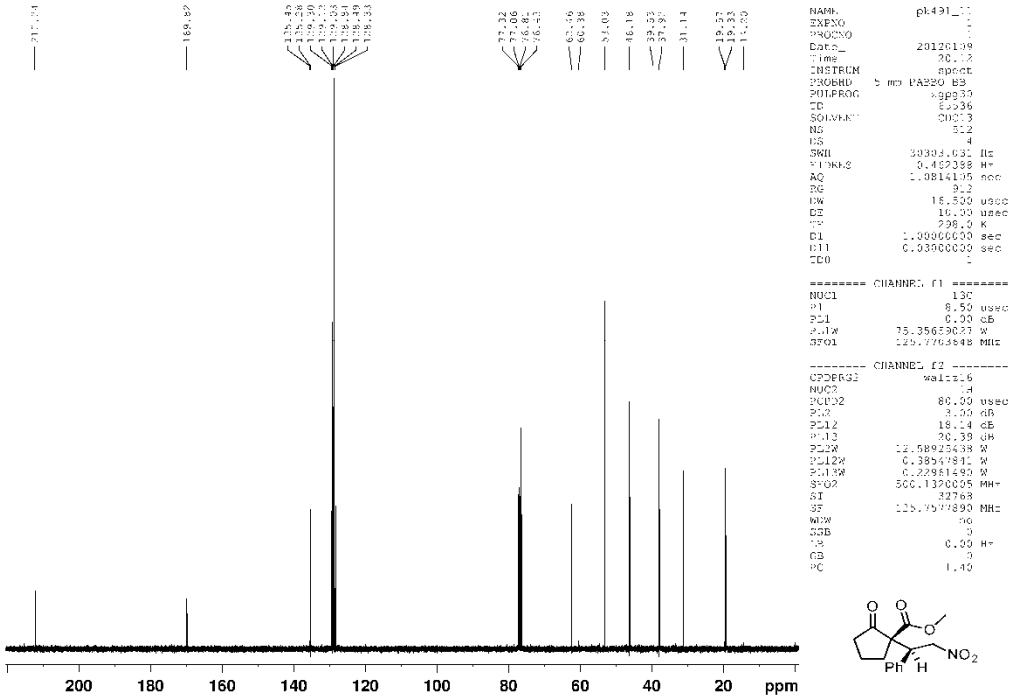

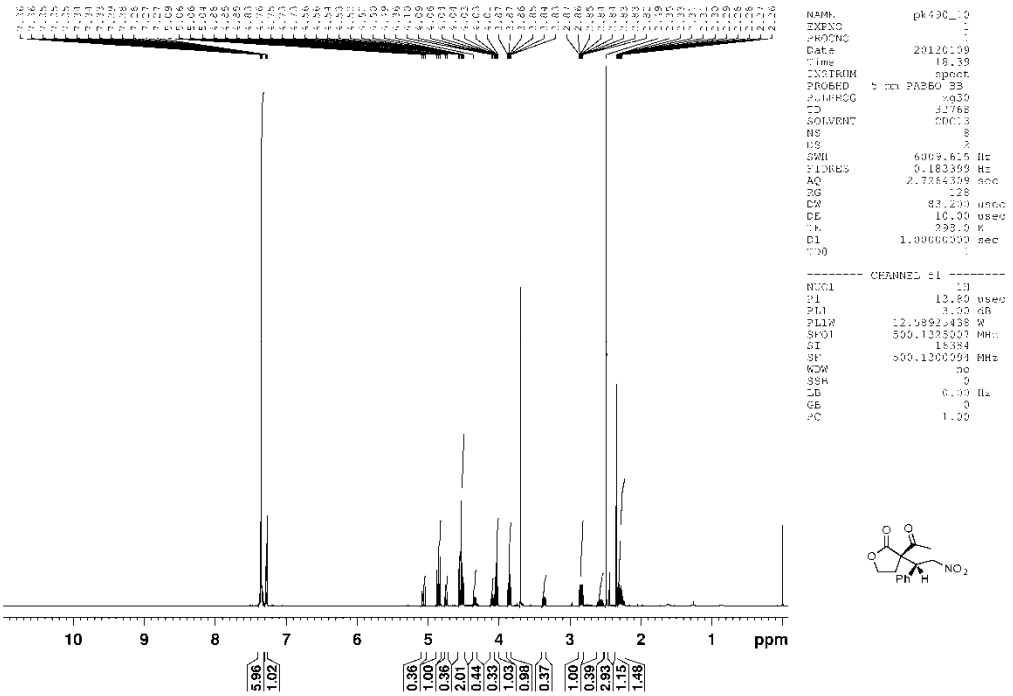

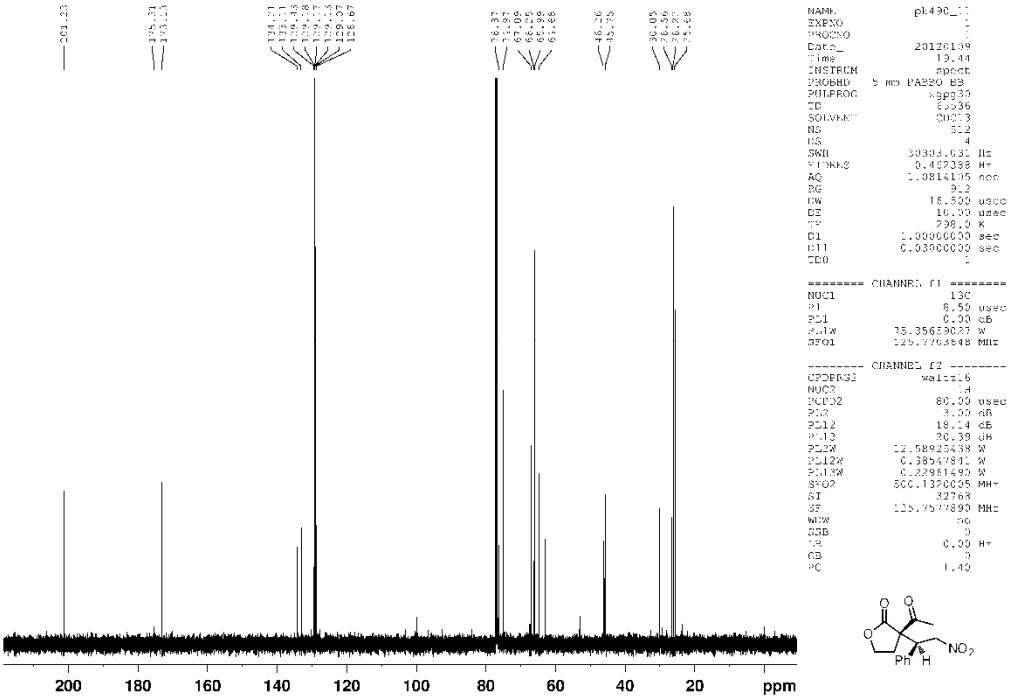

Paper C

Continuous Flow, Highly Enantioselective Michael Additions Catalyzed by a PS-Supported Squaramide

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Continuous Flow, Highly Enantioselective Michael Additions Catalyzed by a PS-Supported Squaramide

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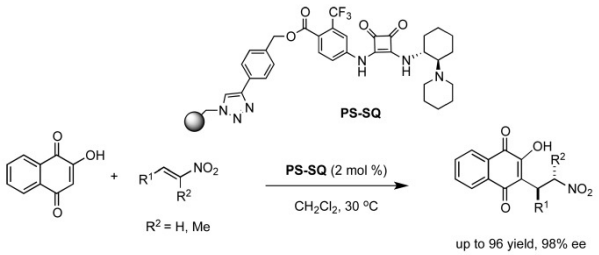
ABSTRACT



A polystyrene (PS) supported bifunctional squaramide organocatalyst promotes fast Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes with very high enantioselectivities at low catalyst loadings. The polystyrene supported catalyst can be recycled up to 10 times without any decrease in enantioselectivity (average 96% ee) and adapted to continuous flow operation (24 h). A single flow experiment involving six different nitroalkenes in a sequential manner highlights the applicability of this methodology for rapid access to chemical diversity.

The past few years have witnessed a significant increase in the popularity of supported chiral catalysts.[1] The costs associated with immobilization of catalytically active species can be compensated by the advantages inherent to this strategy: ease of recovery and reuse of the catalyst and, in optimal cases, the possibility of implementing continuous flow processes.[2]

In particular, chiral organocatalysts have proven to be good candidates for immobilization,[3] due to their robustness and their independence of metal *cofactors*, which suppresses the possibility of their deactivation by metal leaching. Thus,

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different organocatalysts have been supported on a variety of inorganic materials and magnetic nanoparticles[4] and, most successfully, on polystyrene (PS) and other organic polymers,[5] and continuous flow processes yielding highly enantioenriched products have been implemented with their use.[6]

We have recently introduced the polystyrene-supported bifunctional squaramide **PS-SQ** (Figure 1) for the Michael addition of β-dicarbonyl compounds to nitroalkenes.[7] We reasoned that, given the fact that the catalytic performance of squaramides[8] is based on hydrogen bonding rather than in covalent interactions, **PS-SQ** would be particularly robust toward deactivation by off-cycle processes and thus appropriate for long-term operation under flow conditions. We wish to report in this letter the development of a continuous flow, highly enantioselective Michael addition based on **PS-SQ** and the implementation with its use of a device for the sequential preparation of a library of enantiopure adducts.

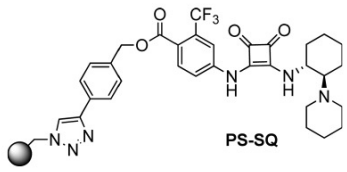
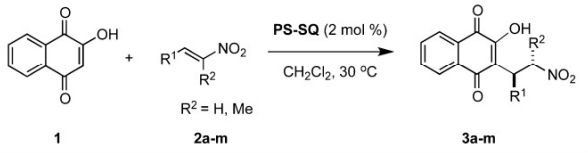


Figure 1. PS-supported squaramide organocatalyst.

Even if a highly enantioselective supported catalyst has been developed,[7] an additional condition is required for its practical use in flow: the reactions have to be fast to allow complete conversion of the reactants with reduced amounts of catalyst and short residence times. To satisfy this, we decided to use 2-hydroxy-1,4-naphthoquinone (**1**) as a Michael donor[9] in front of nitroalkenes under catalysis by our polystyrene-supported squaramide.[10] Du and co-workers have shown[9f] that monomeric squaramides efficiently catalyze the considered Michael addition.

The reaction between **1** and *trans*-β-nitrostyrene using CH_2Cl_2 as the solvent turned out to be fast and clean, and full conversions were recorded in very short times. Remarkably, by employing 5 mol % of the supported catalyst the reaction was complete in less than 20 min yielding **3a** in 96% yield and 97% ee. By lowering the catalyst loading to only 2 mol %, the same results were achieved in 45 min (Table 1, entry 1). These conditions were considered as satisfactory and were used for the rest of the batch study.

Table 1. Michael Addition of 2-Hydroxy-1,4-naphthoquinone with Nitroalkenes[a]



entry	R	product	time (h)	yield (%)[b]	ee (%)[c]
1	C_6H_5	**3a**	0.75	96	97
2	4-BrC_6H_4	**3b**	1	84	96
3	4-$MeOC_6H_4$	**3c**	1	89	93
4	2-BrC_6H_4	**3d**	1	87	94
5	3,4-(OCH_2O)-C_6H_3	**3e**	3	87	95
6	2-$MeOC_6H_4$	**3f**	2	89	91
7	2-thienyl	**3g**	2	90	96
8	2-furanyl	**3h**	2.5	94	95
9	4-MeC_6H_4	**3i**	1	87	96
10	4-FC_6H_4	**3j**	1	95	95
11	4-ClC_6H_4	**3k**	1	98	95
12	2-phenylethyl	**3l**	1.5	91	98
13[d]	C_6H_5	**3m**	18	56	98

[a] **1** (0.2 mmol), **2a**–**m** (0.2 mmol), **PS-SQ** (2 mol %) in CH_2Cl_2 (0.5 mL) at 30 °C. [b] Isolated yield. [c] By HPLC. [d] R^2 = Me, dr = 92:8.

A series of β-nitrostyrenes bearing either electron-withdrawing or -donating groups, as well as some 2-hetarylnitroethylenes, were tested in the reaction (Table 1), and in all cases products were obtained with very high yields and enantioselectivities in short reaction times. The reaction of

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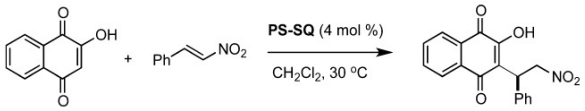
(10) For squaramide catalysts in nitro group activation, see: (c) Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450. (d) Bae, H. Y.; Some, S.; Lee, J. H.; Kim, J.-Y.; Song, M. J.; Lee, S.; Zhang, Y. J.; Song, C. E. *Adv. Synth. Catal.* **2011**, *353*, 3196. (e) Bae, H. Y.; Some, S.; Oh, J. S.; Lee, Y. S.; Song, C. E. *Chem. Commun.* **2011**, *47*, 9621. (f) Marcos, V.; Alemán, J.; Garcia Ruano, J. L.; Marini, F.; Tiecco, M. *Org. Lett.* **2011**, *13*, 3052. (g) Yang, W.; Du, D.-M. *Chem. Commun.* **2011**, *47*, 12706. (h) Palacio, C.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 2849.

para-substituted nitrostyrenes was completed within 1 h with excellent results (entries 2, 3, 9, 10, 11) regardless of the electronic nature of the substituent. Heterocyclic nitroalkenes bearing a furan and a thiophene moiety were also found to be good substrates for this reaction (entries 7, 8). The usually challenging aliphatic nitroalkenes also took part in the reaction as exemplified by 1-nitro-4-phenyl-1-butene, which reacted with **1** to give rise to the desired product in 91% yield and 98% ee (entry 12).

Table 2. Recycling of the **PS-SQ** in Michael Addition of **1** to **2a** in Batch[a]



1 2a 3a

run	time (min)	yield (%)[b]	ee (%)[c]
1	20	97	96
2	30	90	96
3	75	90	96
4	90	87	95
5	90	77	96
6	90	85	96
7	90	74	96
8	90	68	96
9	90	76	96
10	90	67	96

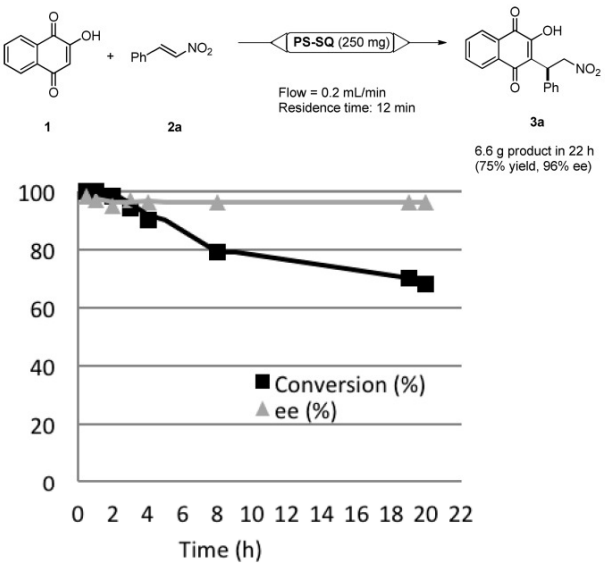
[a] The reaction was run with **1a** (0.2 mmol), **2a** (0.2 mmol), and **PS-SQ** (4 mol %) in CH_2Cl_2 (0.5 mL) at 30 °C. [b] Isolated yield. [c] Determined by chiral HPLC.

As we have previously mentioned, the usefulness of supported catalysts is associated with their robustness and, consequently, their capacity to be reused. To test this capacity in **PS-SQ**, we performed a recycling study with the addition of **1** to **2a**. After each run, the resin was simply filtered and washed with CH_2Cl_2 before reuse. Gratifyingly, with only 4 mol % of **1** the system was found to be active in 10 consecutive runs without any decrease in enantioselectivity (Table 2). A slight decrease in activity was observed after the sixth cycle, which can be attributed to etching of the polymeric matrix upon stirring. Overall, the product was obtained with 96% ee and 81% yield, which corresponds to an accumulated TON of 202.

Since **PS-SQ** fulfilled the requisite characteristics of high catalytic activity and robustness, the possibility of performing the same reaction in continuous flow was next tested. The experimental setup consisted of a low-pressure chromatography column with two adjustable endpieces (see Supporting Information for details) which was loaded with the PS-supported squaramide organocatalyst **PS-SQ** and connected to a pump used to feed the reactor with the reagents (Scheme 1).

It is worth emphasizing that, in this particular case, and given the fact that no reaction takes place at all in the

Scheme 1. Michael Addition of **1** to **2a** in Continuous Flow[a]

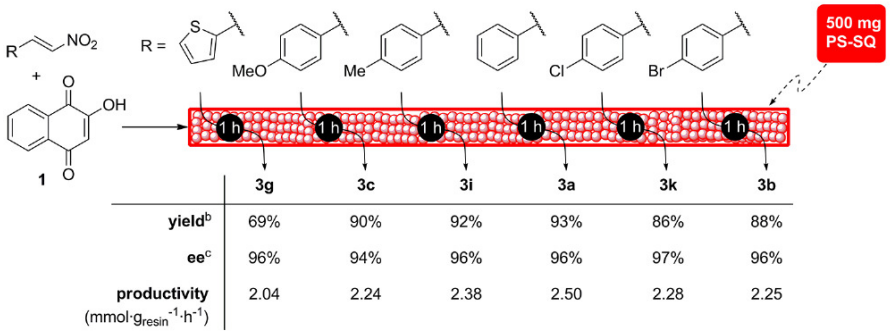


[a] Reaction was performed with 250 mg of resin **PS-SQ** (0.095 mmol) and 270 mL of a 0.1 M solution of the reactants in DCM/THF (10:1) at a 0.2 $mL \cdot min^{-1}$ flow rate.

absence of catalyst, we were even able to pump a solution of both reagents in CH_2Cl_2/THF (10:1),[11] which simplified the setup by avoiding the use of a second pump. The reaction was conducted at room temperature, and preliminary experiments showed that a flow rate of 0.2 $mL \cdot min^{-1}$ was the best compromise between activity and production. Thus, only 0.095 mmol of catalyst **PS-SQ** (250 mg, functionalization $f = 0.38$ $mmol \cdot g^{-1}$) was loaded onto the column and the reaction was performed by using 27 mmol of **1** and a slight excess of **2a** (1.2 equiv). After 20 h, 6.6 g of highly enantioenriched (96% ee) **3a** was obtained, which means a TON of 200 and a productivity of 4.07 $mmol \cdot g_{resin}^{-1} \cdot h^{-1}$. In addition to inherently increased sustainability characteristics arising from workup suppression and highly simplified scale-up, asymmetric continuous flow processes based on supported catalysts can offer an additional advantage: the fast preparation of small libraries of enantiopure compounds. This is a most common need in the early stages of drug discovery that could be readily satisfied by sequential synthesis in a flow device. We reasoned that, for its characteristics of high rate and catalyst robustness, the addition of **1** to a family of nitroolefins **2** mediated by **PS-SQ** could be an ideal scenario to assess the feasibility of this approach. Thus, with a very similar experimental setup we reacted **1** with six different nitroalkenes in a consecutive fashion. Each substrate/2-hydroxy-1,4-naphthoquinone mixture was circulated through the packed-bed reactor for 1 h (flow rate = 0.2 $mL \cdot min^{-1}$), with the column being rinsed by circulation of a mixture of CH_2Cl_2 and THF (10:1) for 30 min between two consecutive substrates. The process was repeated up to

(11) The addition of a small amount of THF was necessary to obtain a homogeneous solution of both reactants.

Scheme 2. Continuous Flow Enantioselective Michael Reaction of Six Different Nitroalkenes with **1**[a]



	3g	3c	3i	3a	3k	3b
yield[b]	69%	90%	92%	93%	86%	88%
ee[c]	96%	94%	96%	96%	97%	96%
productivity ($mmol \cdot g_{resin}^{-1} \cdot h^{-1}$)	2.04	2.24	2.38	2.50	2.28	2.25

[a] Reaction was performed with 500 mg of resin **PS-SQ** (0.171 mmol). A solution of **1** and the corresponding nitroalkene (0.1 M) in 18 mL of CH_2Cl_2/THF (10:1) was pumped at a 0.2 $mL \cdot min^{-1}$ flow rate. See the Supporting Information for experimental details. [b] Isolated yield after 1 h run and 30 min rinse with CH_2Cl_2/THF (10:1). [c] Determined by chiral HPLC.

six times, and the results of the consecutive flow processes are summarized in Scheme 2. Remarkably, the corresponding products **3** were prepared with productivities in the range 2.04–2.50 $mmol \cdot g_{resin}^{-1} \cdot h^{-1}$ which showed no decrease over the whole experiment. Interestingly, this operation mode can be easily adapted to automatic operation with the use of standard equipment, thus allowing the programmable synthesis of small libraries of enantiomerically pure Michael adducts. Interestingly, products of this type are precursors of a variety of bioactive compounds.[9a,b]

In summary the enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes has been promoted by a polystyrene-supported squaramide catalyst, giving rise to the corresponding products in excellent yields and enantioselectivities at very low catalyst loadings. The catalyst has proven highly robust, as exemplified by multiple recycling and reuse with no drop in enantioselectivity. The batch organocatalytic process has been easily transferred to continuous flow operation, which has allowed the sequential preparation of diverse Michael adducts in a single flow experiment with an easily constructed and operated *asymmetric Michael machine*. This illustrates the unique potential of flow processes based on covalently immobilized organocatalysts for the production of libraries of enantiopure compounds. This strategy offers significant potential in areas such as medicinal chemistry or materials science, where small focused libraries of enantiopure compounds are increasingly demanded.

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Supporting Information Available. Detailed experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

Continuous Flow, Highly Enantioselective Michael Additions Catalyzed by a PS-Supported Squaramide

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General Methods

Unless otherwise stated, all commercial reagents were used as received and solvents were used from solvent drying system, all reactions were carried out directly under open air. Merrifield resin (1% DVB, f = 0.53 mmol Cl g^{-1} resin) was obtained from Novabiochem. All flash chromatography was carried out using 60 mesh silica gel and dry-packed columns. The ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H or at 100 MHz and 125 MHz for ^{13}C, respectively. TMS was used as internal standard for ^{1}H NMR and $CDCl_3$ for ^{13}C NMR. Chemical shifts are reported in ppm referred to TMS. FT-IR measurements carried out on a FTIR spectrometer equipped with a DTGS detector, KBr beamsplitter at 4 cm^{-1} resolution. Elemental analyses were performed on a CHNS 932 micro-analyzer. Specific optical rotation measurement was carried out on a polarimeter equipped with a PMT detector using the Sodium line at 589 nm. High performance liquid chromatography (HPLC) was performed by using Chiralpak IA, and IC columns and guard columns. Racemic standard products were prepared using DABCO (20 mol%) as catalyst in order to establish HPLC conditions. Catalyst **PS-SQ** was synthesized according to the reported procedures.[1]

General procedure for the Michael reaction

To a solution of squaramide organocatalyst **PS-SQ** (11.5 mg, 0.004 mmol, 2 mol%, f = 0.38 mmol·g^{-1}) in CH_2Cl_2 (0.5 mL) was added nitroolefin (0.2 mmol) and 2-hydroxy-1,4-naphthoquinone (0.2 mmol). Reactions were monitored by TLC until the consumption of starting compounds, and then the reaction mixture was directly purified by column chromatography on silica gel to afford the Michael product.

General procedure for the recycling reactions in batch conditions

To a solution of squaramide organocatalyst **PS-SQ** (23.0 mg, 0.008 mmol, 4 mol%, f = 0.38 mmol·g^{-1}) in CH_2Cl_2 (0.5 mL) was added nitroolefin (0.2 mmol) and 2-hydroxy-1,4-naphthoquinone (0.2 mmol). Reactions were monitored by TLC until the consumption of starting compounds. Then the reaction mixture was filtered, and washed with 15 mL of CH_2Cl_2. After that the filtrate was concentrated at

reduced pressure and purified by column chromatography on silica gel to afford the Michael product.

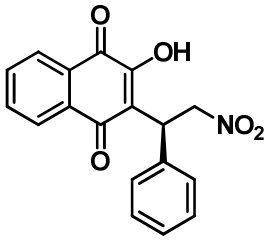
Description of the experimental setup for the continuous flow process

The packed bed reactor consisted of a vertically mounted and fritted low-pressure glass chromatography column (10 mm bore size and up to maximal 70 mm of adjustable bed height) loaded with **PS-SQ** (0.25 g, 0.095 mmol, f = 0.38 mmol·g^{-1}). At the start, CH_2Cl_2/THF (10:1) was flushed for half an hour at 0.2 mL·min^{-1} flow rate to swell the resin. After that, the solvent channel was switched to a solution of 2-hydroxy-1,4-naphthoquinone (27.0 mmol, 4.79 g) and *trans*-β-nitrostyrene (32.4 mmol, 4.83 g) in 270 mL CH_2Cl_2/THF (10:1) of this solution were pumped to the reactor with a flow rate 0.2 mL·min^{-1}. The reactor outlet was connected to a receiving flask where the product was collected. After 22 h flow was stopped and **PS-SQ** washed with CH_2Cl_2/THF (10:1) solvent system for an hour. Conversion and enantioselectivity of the formed product were determined by ^{1}H NMR and HPLC analysis of periodically collected samples. In the end, collected solution was concentrated at reduced pressure and purified by flash chromatography on silica gel.

Description of the experimental setup for the continuous flow process with different substrates

The packed bed reactor was loaded with swollen resin **PS-SQ** (0.50 g, 0.19 mmol, f = 0.38 mmol·g^{-1}) in CH_2Cl_2/THF (10:1) and flushed half an hour with the same solvent mixture at 0.2 mL·min^{-1} flow rate. After the resin was conditioned, the solvent channel was switched to a solution of 2-hydroxy-1,4-naphthoquinone (1.80 mmol) and the corresponding nitroalkene (1.80 mmol) in 18 mL CH_2Cl_2/THF (10:1) and pumped through the reactor with a flow rate of 0.2 mL·min^{-1}. The reactor outlet was connected to a receiving flask where the product was collected. After 1 h, the flow was switched to a washing solvent CH_2Cl_2/THF (10:1) to clean the resin for half an hour. This process was repeated for each nitroalkene. Conversion and enantioselectivity of the product were determined by ^{1}H NMR and HPLC analysis

of periodically collected samples. In the end, collected solutions were concentrated at reduced pressure and purified by flash chromatography on silica gel.

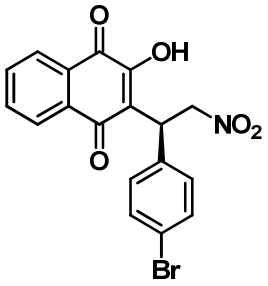


(*S*)-2-Hydroxy-3-(2-nitro-1-phenylethyl)naphthalene-1,4-dione (3a)[2]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (dd, *J* = 6.9, 13.4 Hz, 1H), 5.31 (dd, *J* = 6.8, 9.1 Hz, 1H), 5.47 (dd, *J* = 9.1, 13.4 Hz, 1H), 7.24-7.32 (m, 3H), 7.46 (d, *J* = 7.2 Hz, 2H), 7.68 (dt, *J* = 1.3, 7.5 Hz, 1H), 7.76 (dt, *J* = 1.3, 7.5 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, CDCl3): 39.7, 76.4, 120.8, 126.3, 127.2, 127.8, 128.3 (×2), 129.0 (×3), 132.6, 133.3, 135.4, 137.5, 153.2, 181.1, 183.7.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (90:5:5), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 17.8 (major), 23.9 min (minor).

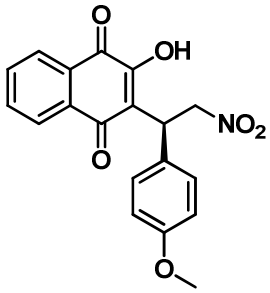


(*S*)-2-(1-(4-Fluorophenyl)-2-nitroethyl)-3-hydroxynaphthalene-1,4-dione (3b)[2]

^{1}H NMR (400 MHz, DMSO-d_6): δ 5.17 (t, *J* = 7.7 Hz, 1H), 5.33-5.28 (m, 1H), 5.45 (dd, *J* = 8.3, 13.7 Hz, 1H), 7.34(d, *J* = 8.5Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.76 (t, *J* = 7.4 Hz, 1H), 7.82 (t, *J* = 7.4 Hz, 1H), 7.97-7.94 (m, 2H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): 38.5, 76.9, 120.1, 120.6, 126.2, 126.4, 130.3, 130.5, 131.8, 132.5, 133.6, 135.2, 138.8, 158.6, 181.8, 183.6.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (85:14:1), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 25.6 (major), 26.6 min (minor).

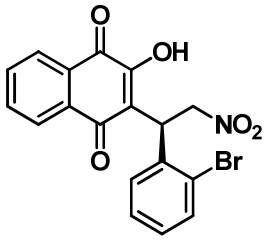


(*S*)-2-Hydroxy-3-(1-(4-methoxyphenyl)-2-nitroethyl)- naphthalene-1,4-dione (3c)[2]

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.76 (s, 3H), 5.11 (dd, *J* = 6.9, 13.3 Hz, 1H), 5.25 (dd, *J* = 7.0, 9.0 Hz, 1H), 5.43 (dd, *J* = 9.0, 13.3 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.69 (dt, *J* = 1.3, 7.6 Hz, 1H), 7.77 (dt, *J* = 1.3, 7.6 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 39.0, 55.3, 76.6, 114.3, 121.1, 126.3, 127.3, 129.0, 129.4, 129.5, 132.7, 133.3, 135.4, 152.9, 159.2, 181.2, 183.3.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (92:4:4), flow rate = 0.6 mL/min, wavelength = 254 nm, r_t = 68.4 (major), 70.4 min (minor).

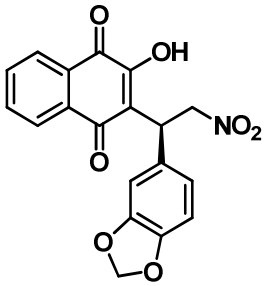


(*R*)-2-(1-(2-Bromophenyl)-2-nitroethyl)-3-hydroxynaphthalene-1,4-dione (3d)[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (dd, *J* = 5.8, 13.7 Hz, 1H), 5.42 (dd, *J* = 10.4, 13.9 Hz, 1H), 5.70 (dd, *J* = 5.7, 10.4 Hz, 1H), 7.13 (dt, *J* = 1.5, 7.8 Hz, 1H), 7.27-7.23 (m, 1H), 7.41 (dd, *J* = 1.6, 7.8 Hz, 1H), 7.60 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.80-7.69 (m, 2H), 8.13-8.09 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 39.9, 74.9, 119.6, 124.6, 126.4, 127.3, 127.9, 129.0, 129.4, 129.6, 132.7, 133.3, 133.6, 135.6, 136.2, 154.0, 181.0, 183.8.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (90:9:1), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 23.2 (major), 24.1 min (minor).



(*S*)-2-(1-(Benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)-3hydroxy-naphthalene-1,4-dione (3e)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (dd, *J* = 7.1, 13.1 Hz, 1H), 5.22 (t, *J* = 7.1, 15.6 Hz, 1H), 5.38 (dd, *J* = 8.4, 13.1 Hz, 1H), 5.90 (dd, *J* = 1.2, 4.0 Hz, 2H), 6.72 (d, *J* = 8.1 Hz, 1H). 6.93 (dd, *J* = 2.1, 7.8 Hz, 1H), 6.97 (d, *J* = 1.7 Hz, 1H), 7.67 (dt, *J* = 1.3, 7.5 Hz, 1H), 7.79-7.75 (m, 2H), 8.05 (dd, *J* = 1.4, 7.6 Hz, 1H), 8.10 (dd, *J* = 1.4, 7.8 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 39.5, 76.6, 101.2, 108.6, 108.7, 120.9, 121.8, 126.3, 127.2, 129.0, 131.1, 132.6, 133.3, 135.4, 147.2, 148.0, 153.0, 181.1, 183.7.

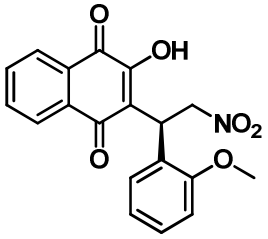
HRMS (ESI): *m*/*z* calcd. for $C_{19}H_{12}NO_7$ $[M - H]^-$ 366.0621, found 366.0619.

$[\alpha]_D^{26}$ = +2.29 (*c* 7.40, $CHCl_3$)

m.p. 136-138 °C.

IR (ATR): ν = 3229, 2891, 1673, 1635, 1546, 1271, 1235, 1038, 790 cm^{-1}.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (88:6:6), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 29.9 (major), 49.8 min (minor).



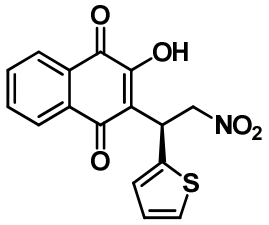
(*S*)-2-Hydroxy-3-(1-(2-methoxyphenyl)-2-nitroethyl)-naphthalene-1,4-dione (3f)[3]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H), 4.96 (dd, *J* = 5.6, 13.6 Hz, 1H), 5.41 (dd, *J* = 10.2, 13.6 Hz, 1H), 5.65 (dd, *J* = 5.6, 10.2 Hz, 1H), 6.90-6.86 (m, 2H),

7.26-7.22 (m, 2H), 7.68 (dt, *J* = 1.3, 6.2 Hz, 1H), 7.71 (s, 1H), 7.76 (dt, *J* = 1.4, 6.2 Hz, 1H), 8.11- 8.07 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 34.2, 55.6, 75.4, 110.9, 120.5, 120.7, 124.9, 126.3, 127.2, 128.8, 129.0, 129.1, 132.9, 133.1, 135.3, 154.0, 156.9, 181.2, 183.8.

HPLC analysis: Chiralpak IC Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (75:23:2), flow rate = 0.7 mL/min, wavelength = 254 nm, r_t = 13.7 (major), 14.4 min (minor).

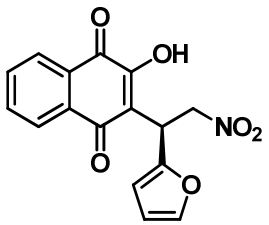


(*S*)-2-Hydroxy-3-(2-nitro-1-(thiophen-2-yl)ethyl)naphthalene-1,4-dione (3g)[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13 (dd, *J* = 6.8, 13.5 Hz, 1H), 5.43 (dd, *J* = 8.9, 13.5 Hz, 1H), 5.61 (dd, *J* = 6.6, 9.0 Hz, 1H), 6.93 (dd, *J* = 3.5, 5.1 Hz, 1H), 7.10-7.11 (m, 1H), 7.20 (dd, *J* = 1.2, 5.1 Hz, 1H), 7.71 (dt, *J* = 1.3, 7.6 Hz, 1H), 7.81-7.77 (m, 2H), 8.08 (d, *J* = 7.5 Hz, 1H), 8.14 (d, *J* = 7.5 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 34.8, 76.7, 119.9, 125.4, 126.4, 126.6, 127.0, 127.2, 129.0, 132.6, 133.4, 135.6, 139.0, 153.1, 181.0, 183.3.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (90:5:5), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 21.2 (major), 22.9 min (minor).

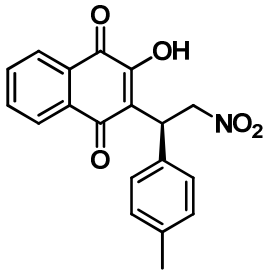


(*S*)-2-(1-(Furan-2-yl)-2-nitroethyl)-3-hydroxynaphthalene-1,4-dione (3h)[2]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.19 (dd, *J* = 6.9, 13.5 Hz, 1H), 5.27 (dd, *J* = 8.6, 13.5 Hz, 1H), 5.47 (t, *J* = 8.7 Hz, 1H), 6.23 (d, *J* = 3.3 Hz, 1H), 6.30 (dd, *J* = 1.8, 3.3 Hz, 1H), 7.32 (dd, *J* = 0.7, 1.8 Hz, 1H), 7.71 (dt, *J* =1.2, 7.6 Hz, 1H), 7.81-7.78 (m, 2H), 8.09 (dd, *J* = 1.4, 7.7 Hz, 1H), 8.14 (dd, *J* = 1.4, 7.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 33.4, 74.7, 107.4, 110.7, 118.0, 126.4, 127.3, 129.0, 132.6, 133.4, 135.6, 142.3, 149.8, 153.9, 181.0, 183.2.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (92:4:4), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 24.1 (major), 27.5 min (minor).

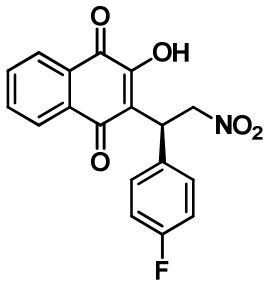


(*S*)-2-Hydroxy-3-(2-nitro-1-(p-tolyl)ethyl)naphthalene-1,4-dione (3i)[2]

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 3H), 5.12 (dd, *J* = 6.8, 13.3 Hz, 1H), 5.28 (dd, *J* = 6.8, 10.4 Hz, 1H), 5.46 (dd, *J* = 9.0, 13.3 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.66-7.78 (m, 3H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.0, 39.3, 76.4, 121.0, 126.3, 127.2, 128.1, 129.0, 129.7, 132.7, 133.2, 134.5, 135.4, 137.7, 153.1, 181.2, 183.7.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (90:5:5), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 20.9 (major), 25.8 min (minor).

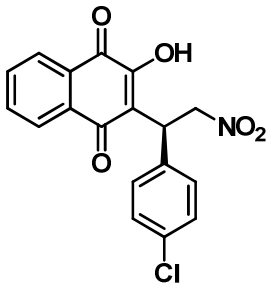


(*S*)-2-(1-(4-Fluorophenyl)-2-nitroethyl)-3-hydroxynaphthalene-1,4-dione (3j)[2]

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (dd, *J* = 6.8, 12.7 Hz, 1H), 5.29 (t, *J* = 15.2 Hz, 1H), 5.40 (dd, *J* = 8.4, 12.7 Hz, 1H), 6.99 (t, *J* = 8.7 Hz, 2H), 7.45 (dd, *J* = 5.2, 8.8 Hz, 2H), 7.70 (dt, *J* = 1.4, 7.6 Hz, 1H), 7.78 (dt, *J* = 1.4, 7.6 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.7 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 39.0, 76.4, 115.9 (d, *J* = 21.3 Hz), 120.6, 126.4, 127.2, 128.9, 130.0 (d, *J* = 8.3 Hz), 130.1, 132.6, 133.3, 133.4, 135.6, 153.3, 162.2 (d, *J* = 246.9 Hz), 181.1, 183.7.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (90:5:5), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 20.5 (major), 23.4 min (minor).

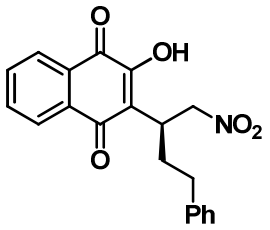


(*S*)-2-(1-(4-Chlorophenyl)-2-nitroethyl)-3-hydroxynaphthalene-1,4-dione (3k)[2]

^{1}H NMR (400 MHz, DMSO-d_6): δ 5.19 (t, *J* = 7.8 Hz, 1H), 5.32 (dd, *J* = 7.5, 13.9 Hz, 1H), 5.43 (dd, *J* = 8.2, 13.8 Hz, 1H), 7.41-7.35 (m, 4H), 7.79 (dt, *J* = 1.4, 7.4 Hz, 1H), 7.85 (dt, *J* = 1.4, 7.4 Hz, 1H), 8.00-7.97 (m, 2H) ppm.

^{13}C NMR (100 MHz, DMSO-d_6): 38.3, 76.9, 120.8, 126.3, 126.4, 129.0 (×2), 130.2 (×3), 130.4, 132.2, 133.9, 135.3, 138.0, 157.1, 181.3, 184.2.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (90:5:5), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 20.4 (major), 21.8 min (minor).

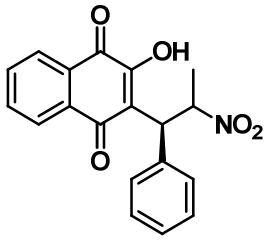


(*S*)-2-Hydroxy-3-(1-nitro-4-phenylbutan-2-yl)naphthalene-1,4-dione (3l)[2]

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.04-1.97 (m, 1H), 2.33-2.25 (m, 1H), 2.61-2.55 (m, 1H), 2.72-2.66 (m, 1H), 4.13-4.07 (m, 1H), 4.71 (dd, *J* = 12.6, 6.2 Hz, 1H), 4.96 (dd, *J* = 12.7, 9.1 Hz, 1H), 7.10-7.04 (m, 3H), 7.17-7.14 (m, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.78 (t, *J* = 7.5 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 31.7, 33.8, 34.8, 77.1, 120.4, 126.1, 126.3, 127.1, 128.2, 128.3, 129.1, 132.8, 133.2, 135.3, 140.9, 153.9, 180.7, 183.9.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (90:9:1), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 23.8 (major), 25.4 min (minor).



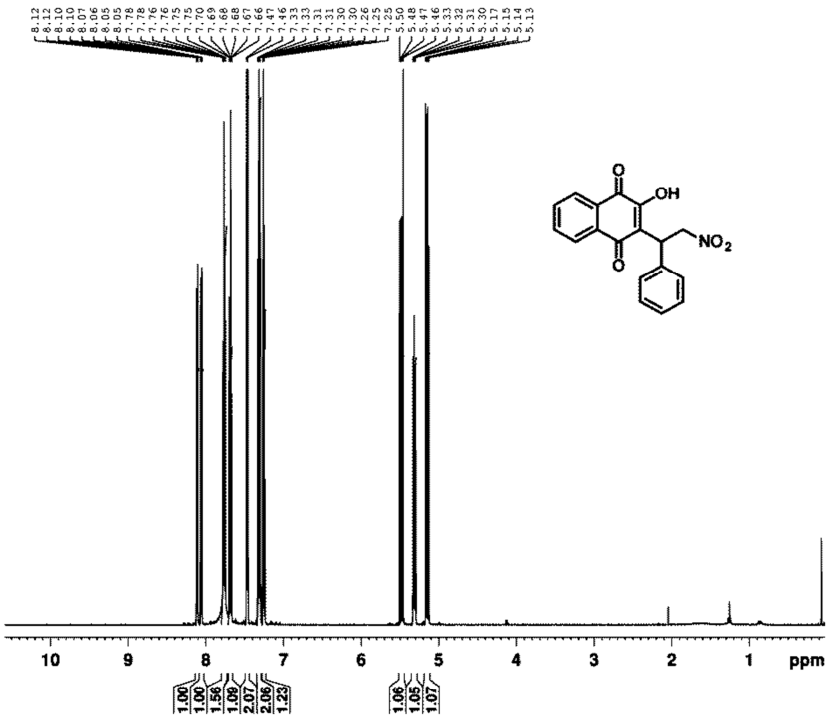
2-Hydroxy-3-((1*S*)-2-nitro-1-phenylpropyl)naphthalene-1,4-dione (3m)[3]

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (d, *J* = 6.7 Hz, 3H), 4.93 (d, *J* = 11.6 Hz, 1H), 6.05-6.12 (m, 1H), 7.24-7.33 (m, 3H), 7.52-7.54 (m, 2H), 7.64 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.73 (dt, *J* = 1.3, 7.5 Hz, 1H), 7.78 (s, 1H), 8.01 (dd, *J* = 1.3, 7.6 Hz, 1H), 8.10 (dd, *J* = 1.0, 7.6 Hz, 1H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 19.7, 46.6, 83.4, 121.2, 126.2, 127.2, 127.9, 129.1, 129.2, 129.9, 132.7, 133.1, 135.3, 137.3, 152.8, 181.1, 183.6.

HPLC analysis: Chiralpak IA Column, Hexane (0.1% TFA)/Dichloromethane/Ethanol (90:5:5), flow rate = 1.0 mL/min, wavelength = 254 nm, r_t = 15.2 (major), 23.9 min (minor).

Spectral data



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PROCNO	1
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PULPROG	zg30
TD	32768
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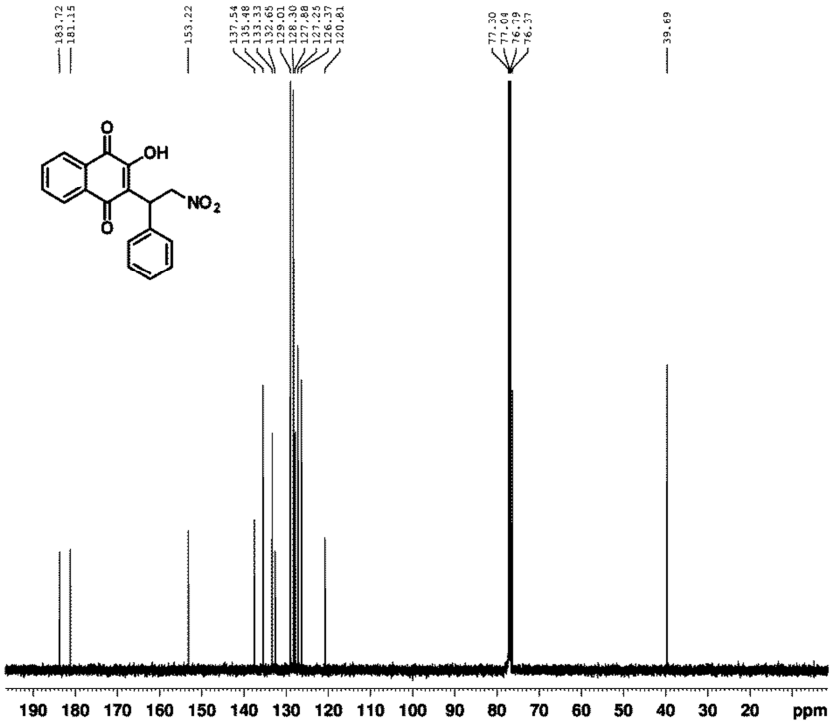
NS	8
DS	2
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7264309 sec
RG	228
DW	83.200 usec
DE	10.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	13.80 usec
PL1	3.00 dB
PL1W	12.58925438 W
SFO1	500.1325007 MHz
SI	16384
SF	500.1300158 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



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PROCNO	1
Date_	20121201
Time	0.23
INSTRUM	spect
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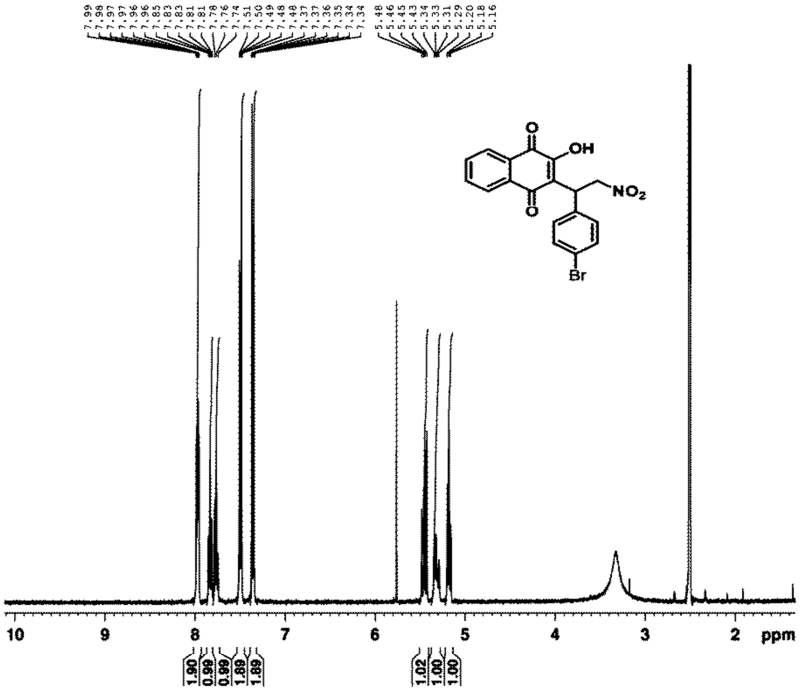
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	30303.031 Hz
FIDRES	0.462388 Hz
AQ	1.0814105 sec
RG	812
DW	16.500 usec
DE	10.00 usec
TE	298.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	8.50 usec
PL1	0.00 dB
PL1W	75.35659027 W
SFO1	125.7703648 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	3.00 dB
PL12	18.14 dB
PL13	20.39 dB
PL2W	12.58925438 W
PL12W	0.38547841 W
PL13W	0.22961490 W
SFO2	500.1320005 MHz
SI	32768
SF	125.7577890 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



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EXPNO	1
PROCNO	1
Date_	20130215
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PULPROG	zg30
TD	32768
SOLVENT	DMSO
NS	8
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	256
DW	104.400 usec
DE	6.00 usec
TE	298.1 K
D1	1.00000000 sec
TD0	1
========	CHANNEL f1 ========
NUC1	1H
P1	14.50 usec
PL1	-2.00 dB
PL1W	23.88643074 W
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SI	16384
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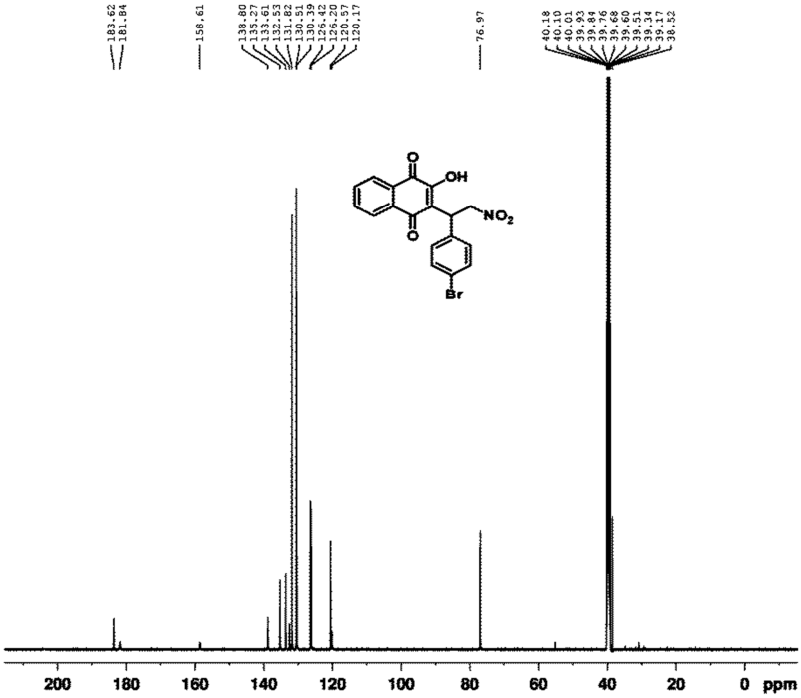
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



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EXPNO	2
PROCNO	1
Date_	20130313
Time	8.18
INSTRUM	spect
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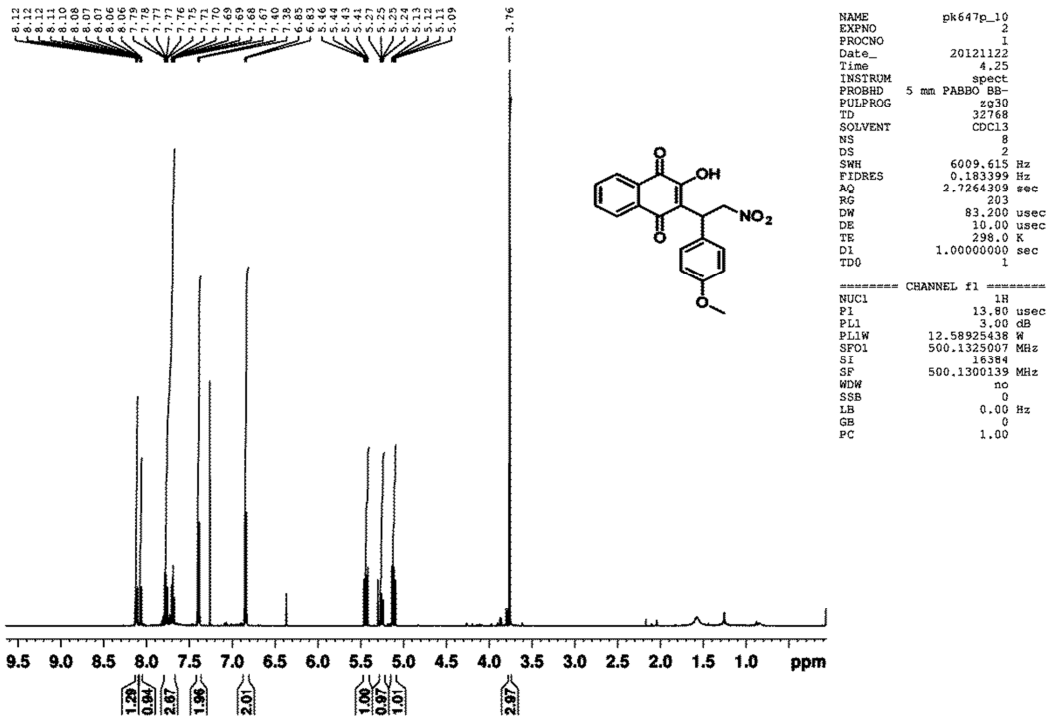
PULPROG	zgpg30
TD	65536
SOLVENT	DMSO
NS	2151
DS	2
SWH	29761.904 Hz
FIDRES	0.454131 Hz
AQ	1.1010548 sec
RG	512
DW	16.800 usec
DE	18.00 usec
TE	298.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
========	CHANNEL f1 ========
SFO1	125.8608968 MHz
NUC1	13C
P1	10.00 usec
SI	32768
SF	125.8483120 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.00



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PROCNO	1
Date_	20121122
Time	4.25
INSTRUM	spect
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PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	8
DS	2
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7264309 sec
RG	203
DW	83.200 usec
DE	10.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
========= CHANNEL f1 =========	
NUC1	1H
P1	13.80 usec
PL1	3.00 dB
PL1W	12.58925438 W
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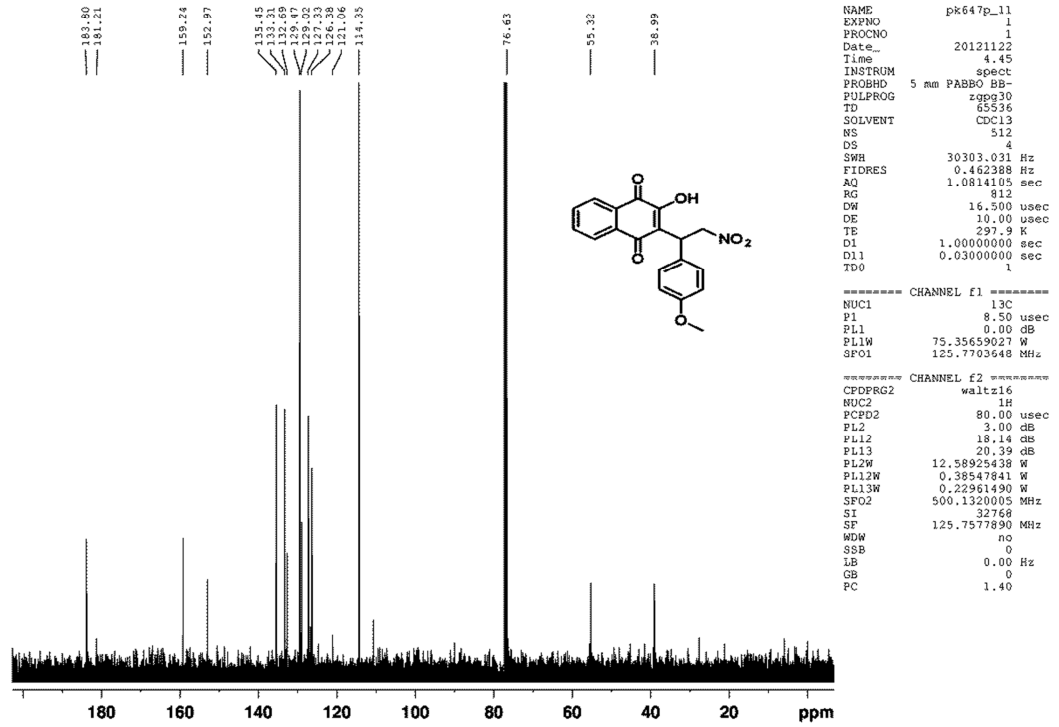
SI	16384
SF	500.1300139 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



NAME	pk647p_11
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PROCNO	1
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INSTRUM	spect
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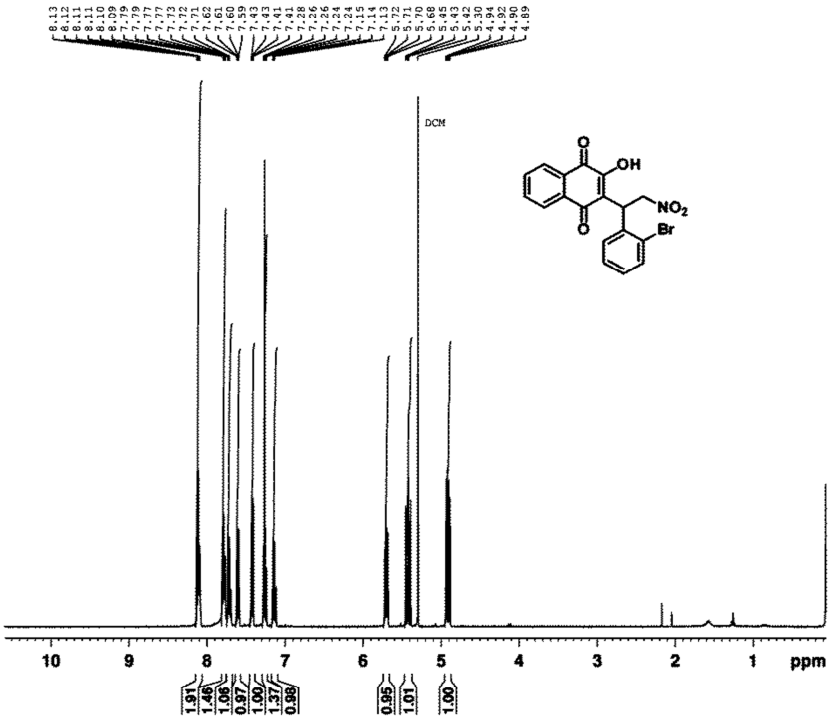
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	30303.031 Hz
FIDRES	0.462388 Hz
AQ	1.0814105 sec
RG	812
DW	16.500 usec
DE	10.00 usec
TE	297.9 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	8.50 usec
PL1	0.00 dB
PL1W	75.35659027 W
SFO1	125.7703648 MHz
========= CHANNEL f2 =========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	3.00 dB
PL12	18.14 dB
PL13	20.39 dB
PL2W	12.58925438 W
PL12W	0.38547841 W
PL13W	0.22961490 W
SFO2	500.1320005 MHz
SI	32768
SF	125.7577890 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

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PROCNO                 1
Date_           20130131
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INSTRUM            spect
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PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                     8
DS                     2
SWH           4789.272 Hz
FIDRES        0.146157 Hz
AQ            3.4210291 sec
RG                   181
DW             104.400 usec
DE               6.00 usec
TE               297.9 K
D1            1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                 1H
P1                14.50 usec
PL1               -2.00 dB
PL1W        23.88643074 W
SFO1        400.1320007 MHz
SI                 16384
SF          400.1300093 MHz
WDW                   no
SSB                    0
LB                0.00 Hz
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PC                1.00
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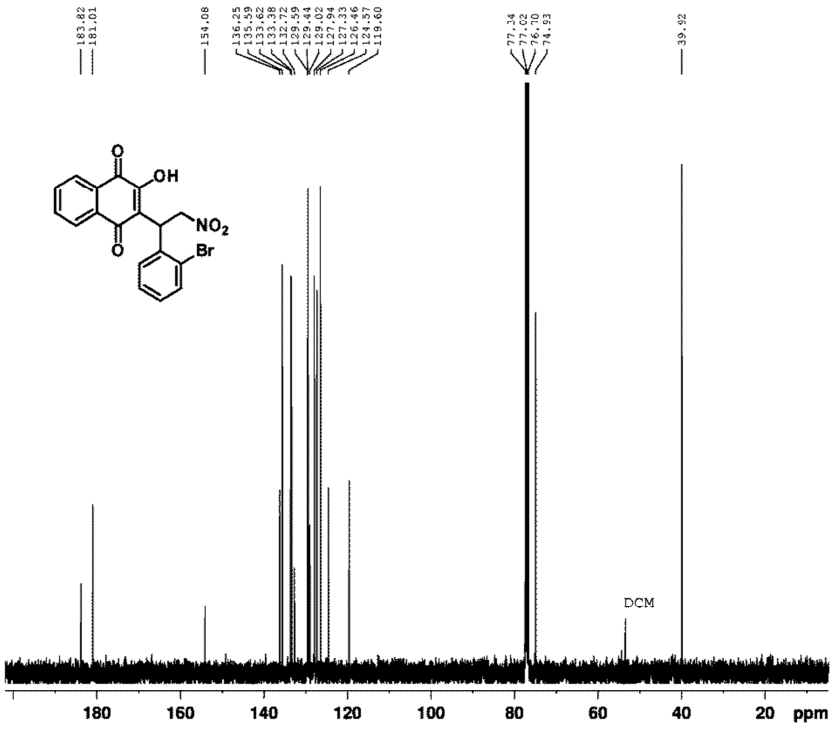


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NAME          pk648pt_11
EXPNO                  1
PROCNO                 1
Date_           20130131
Time               20.30
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                 65536
SOLVENT            CDCl3
NS                   512
DS                     4
SWH          23980.814 Hz
FIDRES        0.365918 Hz
AQ            1.3664756 sec
RG              20642.5
DW               20.850 usec
DE               10.00 usec
TE               298.1 K
D1            1.00000000 sec
D11           0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                13C
P1                10.00 usec
PL1               -3.00 dB
PL1W        75.17808533 W
SFO1        100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                 1H
PCPD2             80.00 usec
PL2               -3.00 dB
PL12              13.00 dB
PL13              13.00 dB
PL2W        30.07123375 W
PL12W        0.75535524 W
PL13W        0.75535524 W
SFO2        400.1316005 MHz
SI                 32768
SF          100.6127690 MHz
WDW                   EM
SSB                    0
LB                1.00 Hz
GB                     0
PC                1.40
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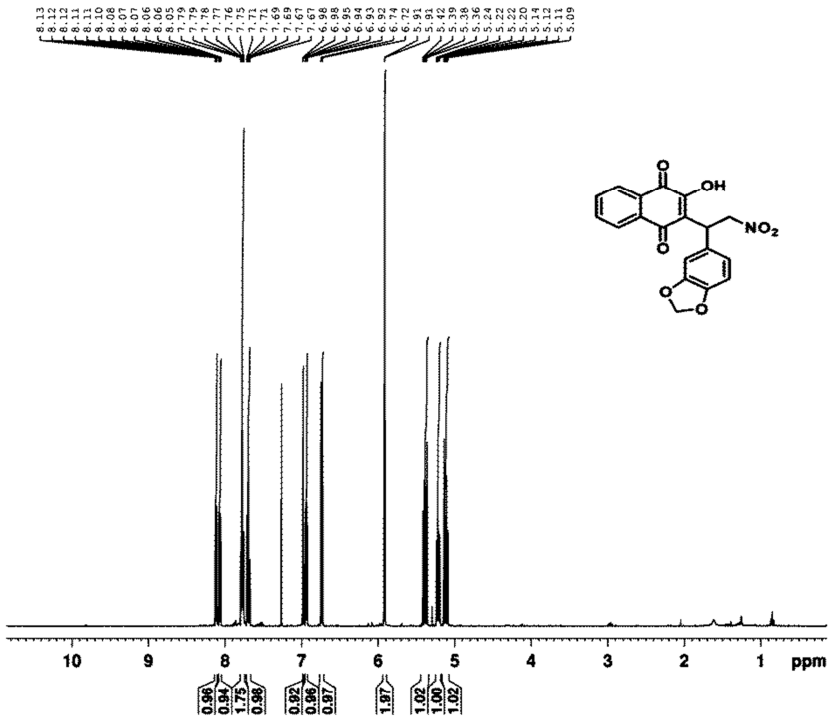

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PROCNO	1
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INSTRUM	spect
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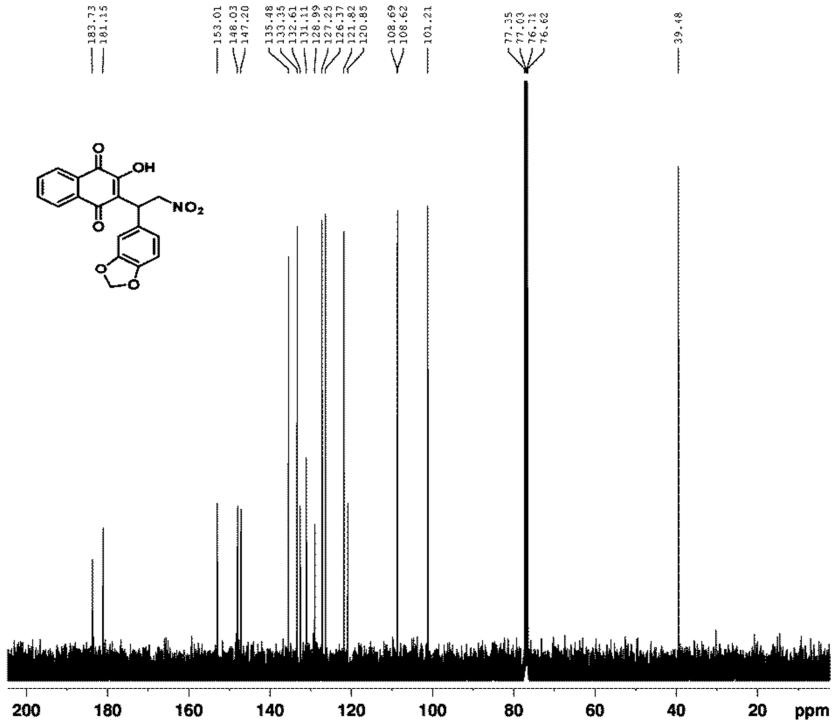
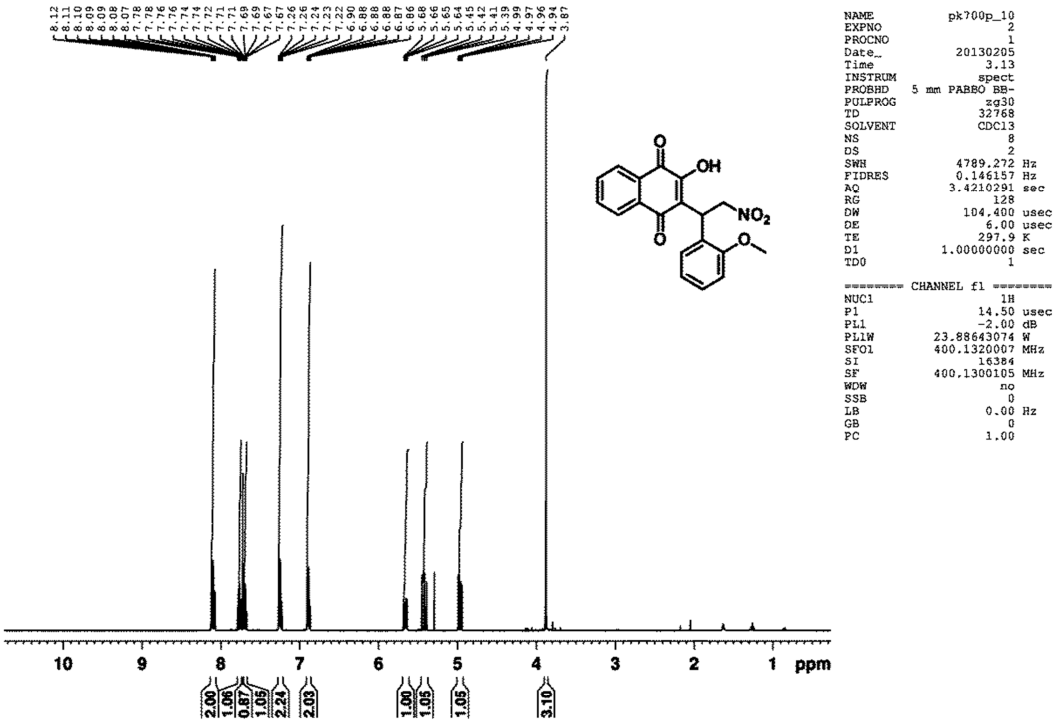
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	8
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	161.3
DW	104.400 usec
DE	6.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	14.50 usec
PL1	-2.00 dB
PL1W	23.88643074 W
SFO1	400.1320007 MHz
SI	16384
SF	400.1300090 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

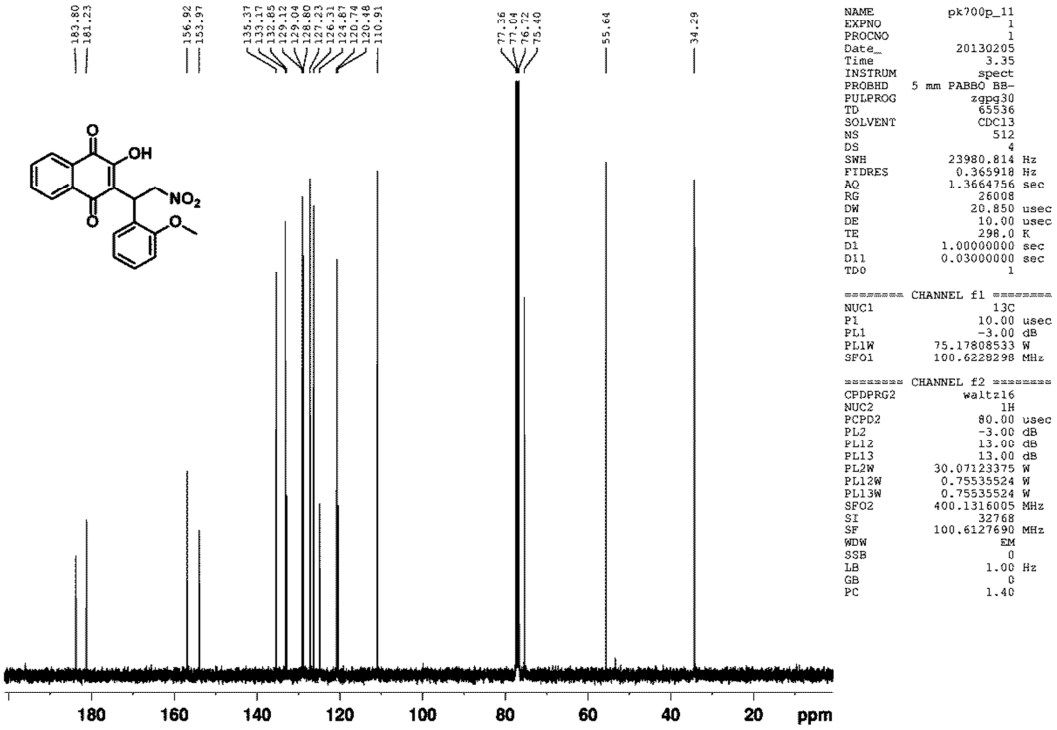


NAME	pk699a_11
EXPNO	3
PROCNO	1
Date_	20130206
Time	16.25
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	76
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	32768
DW	20.850 usec
DE	10.00 usec
TE	298.2 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-3.00 dB
PL1W	75.17808533 W
SFO1	100.6228298 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	13.00 dB
PL13	13.00 dB
PL2W	30.07123375 W
PL12W	0.75535524 W
PL13W	0.75535524 W
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40




```
NAME            pk700p_10
EXPNO                   2
PROCNO                  1
Date_            20130205
Time                3.13
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                      8
DS                      2
SWH              4789.272 Hz
FIDRES           0.146157 Hz
AQ               3.4210291 sec
RG                    128
DW                104.400 usec
DE                  6.00 usec
TE                297.9 K
D1             1.00000000 sec
TD0                     1

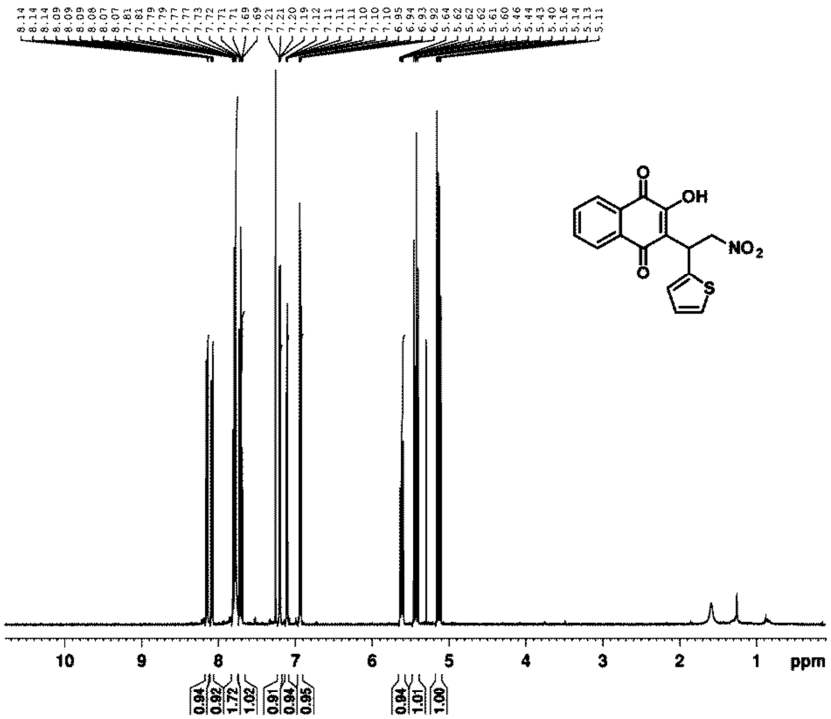
======== CHANNEL f1 ========
NUC1                   1H
P1                  14.50 usec
PL1                 -2.00 dB
PL1W          23.88643074 W
SFO1          400.1320007 MHz
SI                  16384
SF            400.1300105 MHz
WDW                    no
SSB                     0
LB                 0.00 Hz
GB                      0
PC                   1.00
```




```
NAME            pk700p_11
EXPNO                   1
PROCNO                  1
Date_            20130205
Time                3.35
INSTRUM            spect
PROBHD    5 mm PABBO BB-
PULPROG           zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    512
DS                      4
SWH              23980.814 Hz
FIDRES           0.365918 Hz
AQ               1.3664756 sec
RG                    26008
DW                20.850 usec
DE                  10.00 usec
TE                298.0 K
D1             1.00000000 sec
D11            0.03000000 sec
TD0                     1

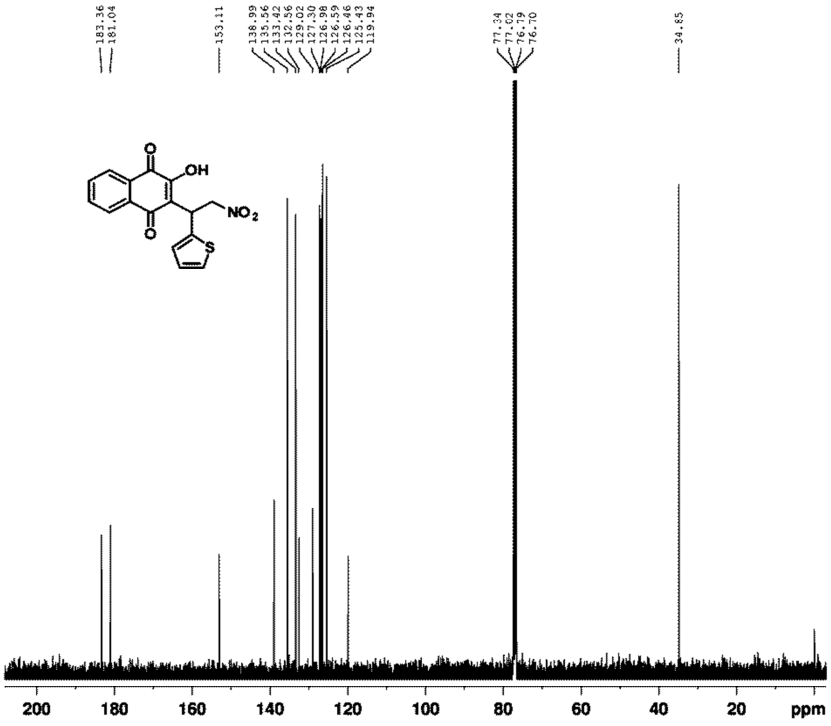
======== CHANNEL f1 ========
NUC1                   13C
P1                  10.00 usec
PL1                 -3.00 dB
PL1W          75.17808533 W
SFO1          100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -3.00 dB
PL12                13.00 dB
PL13                13.00 dB
PL2W          30.07123375 W
PL12W          0.75535524 W
PL13W          0.75535524 W
SFO2          400.1316005 MHz
SI                  32768
SF            100.6127690 MHz
WDW                    EM
SSB                     0
LB                  1.00 Hz
GB                      0
PC                   1.40
```




```
NAME          pk658pt_10
EXPNO                  2
PROCNO                 1
Date_           20130201
Time                1.17
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG             zg30
TD                 32768
SOLVENT            CDCl3
NS                     8
DS                     2
SWH           4789.272 Hz
FIDRES        0.146157 Hz
AQ            3.4210291 sec
RG                   181
DW              104.400 usec
DE                6.00 usec
TE               297.9 K
D1           1.00000000 sec
TD0                    1

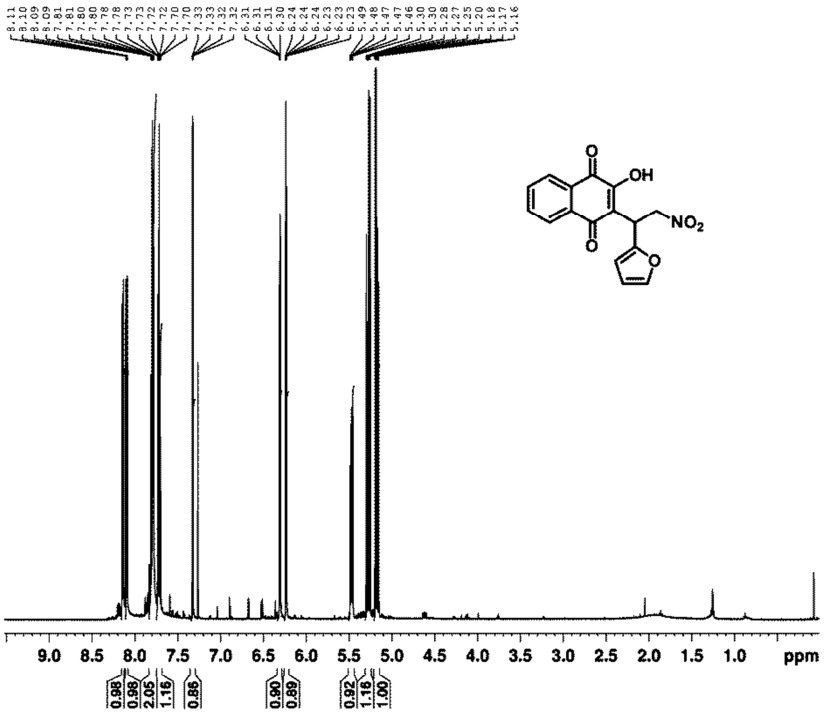
======== CHANNEL f1 ========
NUC1                  1H
P1                 14.50 usec
PL1                -2.00 dB
PL1W        23.88643074 W
SFO1       400.1320007 MHz
SI                 16384
SF         400.1300097 MHz
WDW                   no
SSB                    0
LB                 0.00 Hz
GB                     0
PC                 1.00
```




```
NAME          pk658pt_11
EXPNO                  1
PROCNO                 1
Date_           20130201
Time                1.40
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG          zgpg30
TD                65536
SOLVENT            CDCl3
NS                   512
DS                     4
SWH          23980.814 Hz
FIDRES        0.365918 Hz
AQ            1.3664756 sec
RG                 23170.5
DW                20.850 usec
DE                10.00 usec
TE                298.1 K
D1           1.00000000 sec
D11          0.03000000 sec
TD0                    1

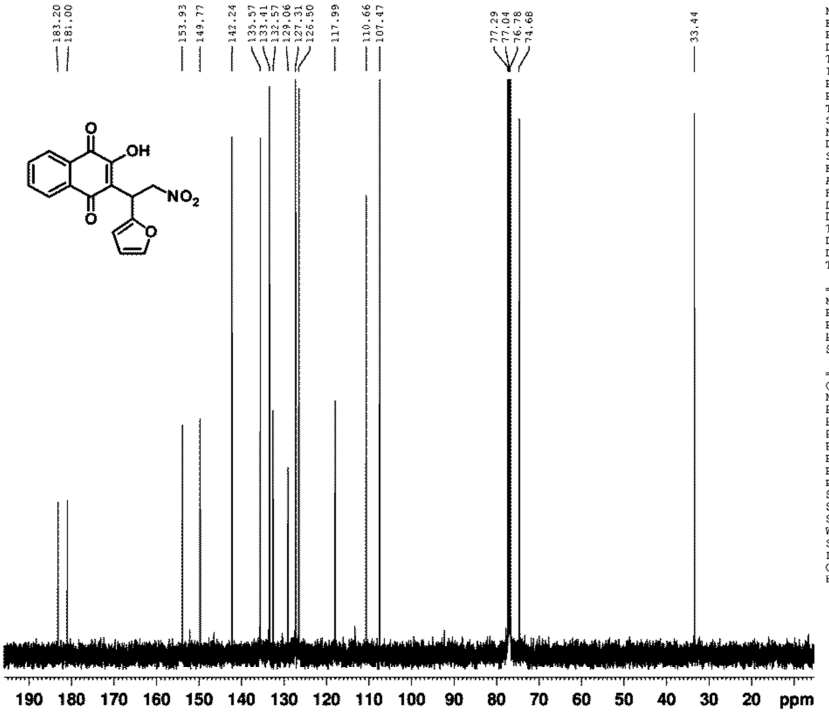
======== CHANNEL f1 ========
NUC1                  13C
P1                 10.00 usec
PL1                -3.00 dB
PL1W        75.17808533 W
SFO1       100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                  1H
PCPD2              80.00 usec
PL2                -3.00 dB
PL12               13.00 dB
PL13               13.00 dB
PL2W        30.07123375 W
PL12W        0.75535524 W
PL13W        0.75535524 W
SFO2       400.1316005 MHz
SI                 32768
SF         100.6127690 MHz
WDW                   EM
SSB                    0
LB                 1.00 Hz
GB                     0
PC                 1.40
```




```
NAME            pk649p_10
EXPNO                   1
PROCNO                  1
Date_            20121121
Time                1.46
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                      8
DS                      2
SWH              6009.615 Hz
FIDRES           0.183399 Hz
AQ               2.7264309 sec
RG                    256
DW                 83.200 usec
DE                 10.00 usec
TE                 298.0 K
D1              1.00000000 sec
TD0                     1

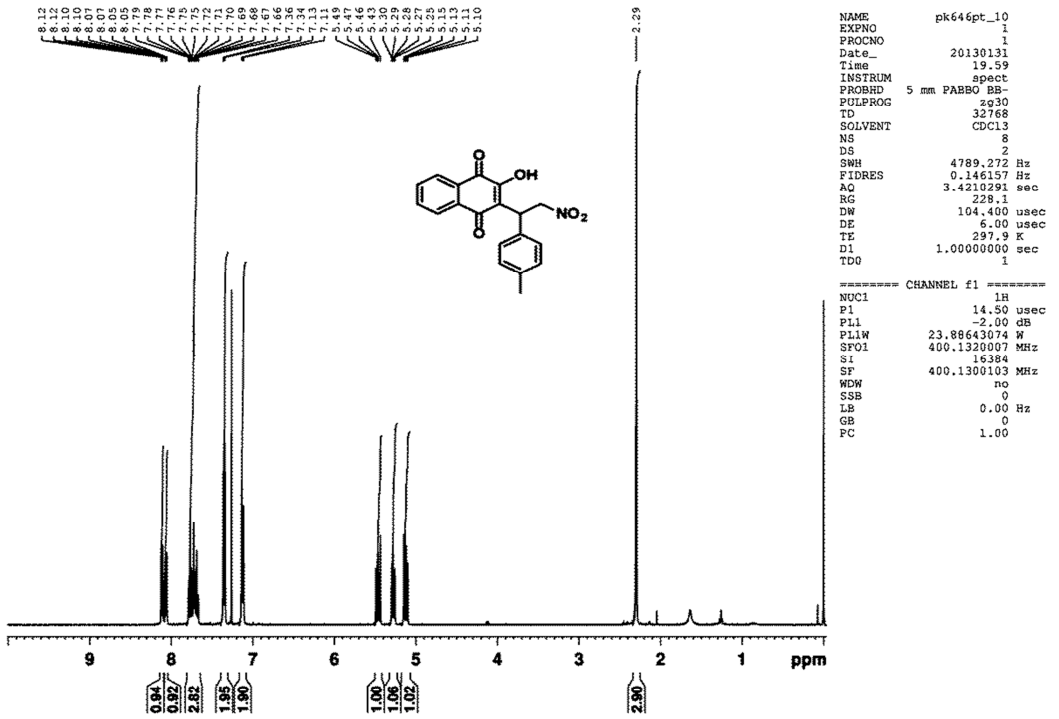
======== CHANNEL f1 ========
NUC1                   1H
P1                  13.80 usec
PL1                  3.00 dB
PL1W          12.58925438 W
SFO1          500.1325007 MHz
SI                  16384
SF            500.1300117 MHz
WDW                    no
SSB                     0
LB                   0.00 Hz
GB                      0
PC                   1.00
```



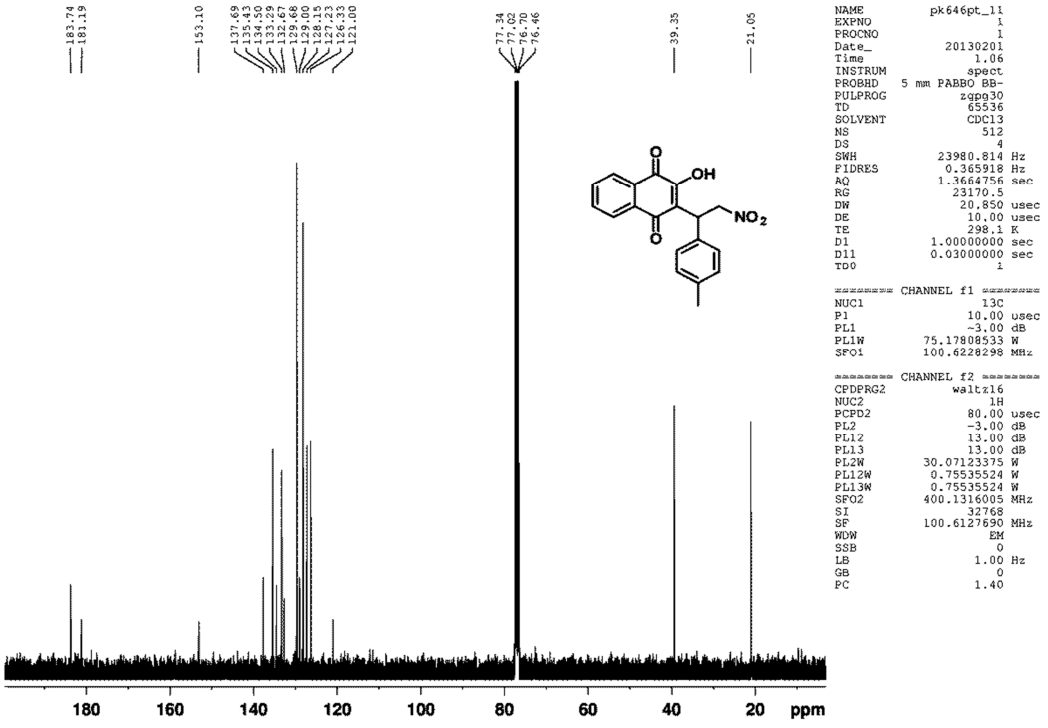

```
NAME            pk649p_11
EXPNO                   1
PROCNO                  1
Date_            20121121
Time                2.06
INSTRUM            spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg30
TD                  65536
SOLVENT             CDCl3
NS                    512
DS                      4
SWH             30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0814105 sec
RG                    812
DW                 16.500 usec
DE                 10.00 usec
TE                 297.9 K
D1              1.00000000 sec
D11             0.03000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                  13C
P1                   8.50 usec
PL1                  0.00 dB
PL1W          75.35659027 W
SFO1          125.7703648 MHz

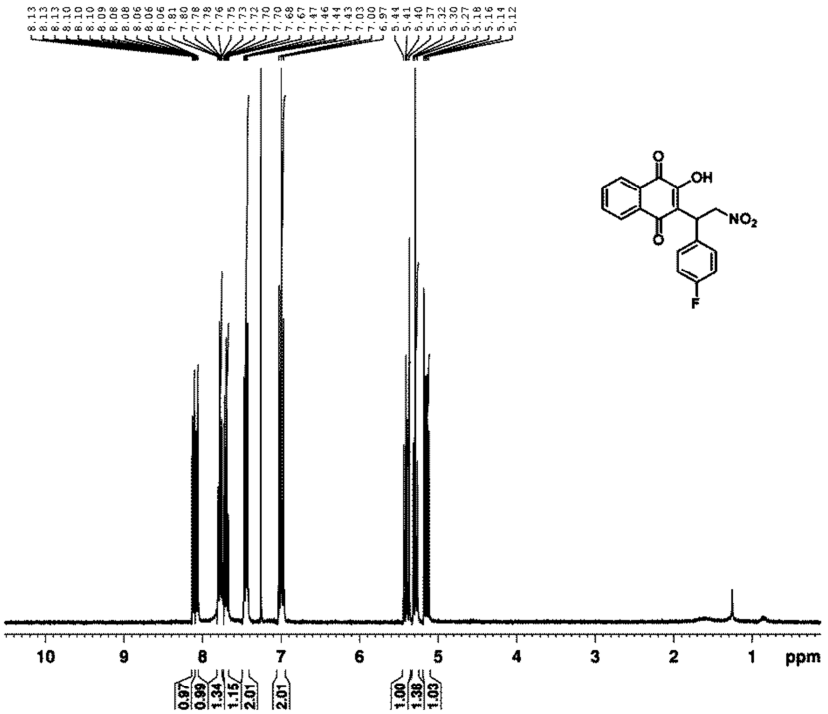
======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              80.00 usec
PL2                  3.00 dB
PL12                18.14 dB
PL13                20.39 dB
PL2W          12.58925438 W
PL12W          0.38547841 W
PL13W          0.22961490 W
SFO2          500.1320005 MHz
SI                  32768
SF            125.7577890 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40
```



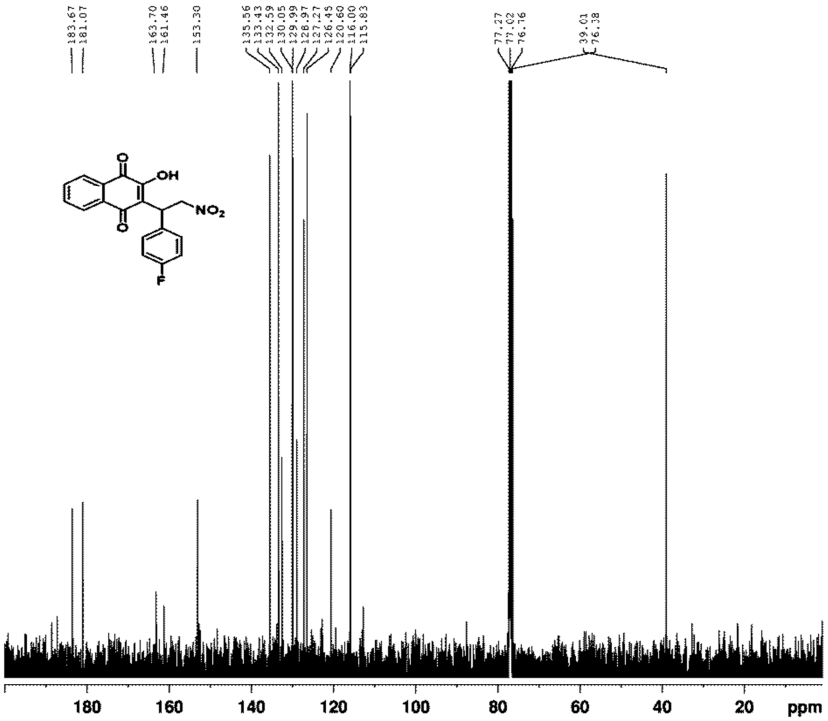
NAME	pk646pt_10
EXPNO	1
PROCNO	1
Date_	20130131
Time	19.59
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	8
DS	2
SWH	4789.272 Hz
FIDRES	0.146157 Hz
AQ	3.4210291 sec
RG	228.1
DW	104.400 usec
DE	6.00 usec
TE	297.9 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	14.50 usec
PL1	-2.00 dB
PL1W	23.88643074 W
SFO1	400.1320007 MHz
SI	16384
SF	400.1300103 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



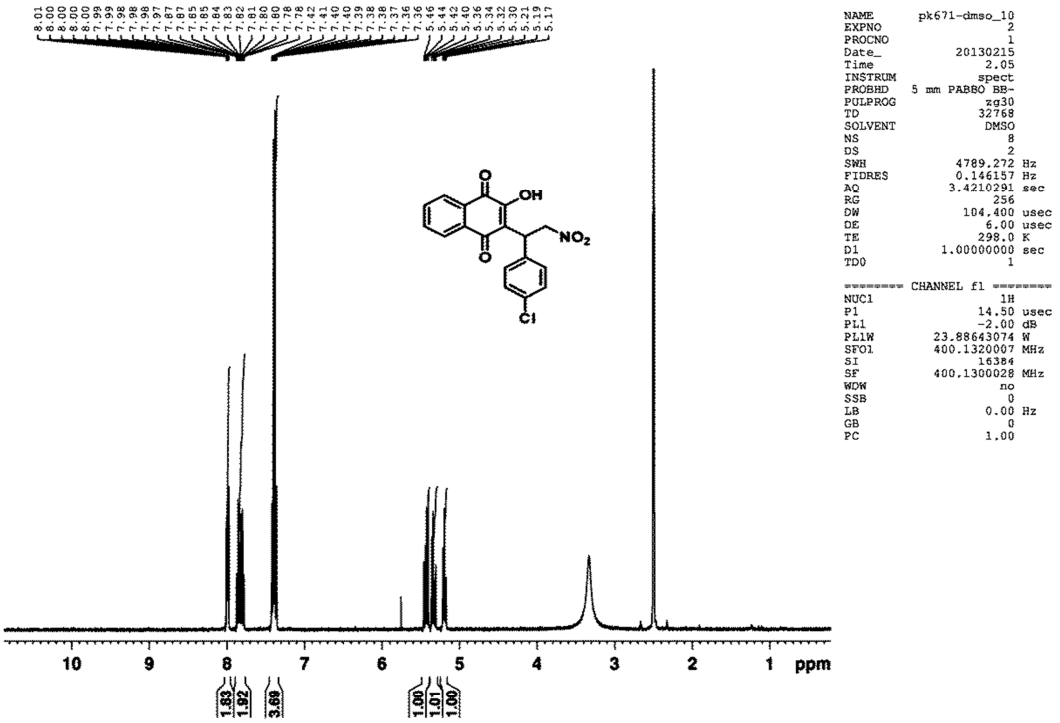
NAME	pk646pt_11
EXPNO	1
PROCNO	1
Date_	20130201
Time	1.06
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	23980.814 Hz
FIDRES	0.365918 Hz
AQ	1.3664756 sec
RG	23170.5
DW	20.850 usec
DE	10.00 usec
TE	298.1 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	10.00 usec
PL1	-3.00 dB
PL1W	75.17808533 W
SFO1	100.6228298 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-3.00 dB
PL12	13.00 dB
PL13	13.00 dB
PL2W	30.07123375 W
PL12W	0.75535524 W
PL13W	0.75535524 W
SFO2	400.1316005 MHz
SI	32768
SF	100.6127690 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

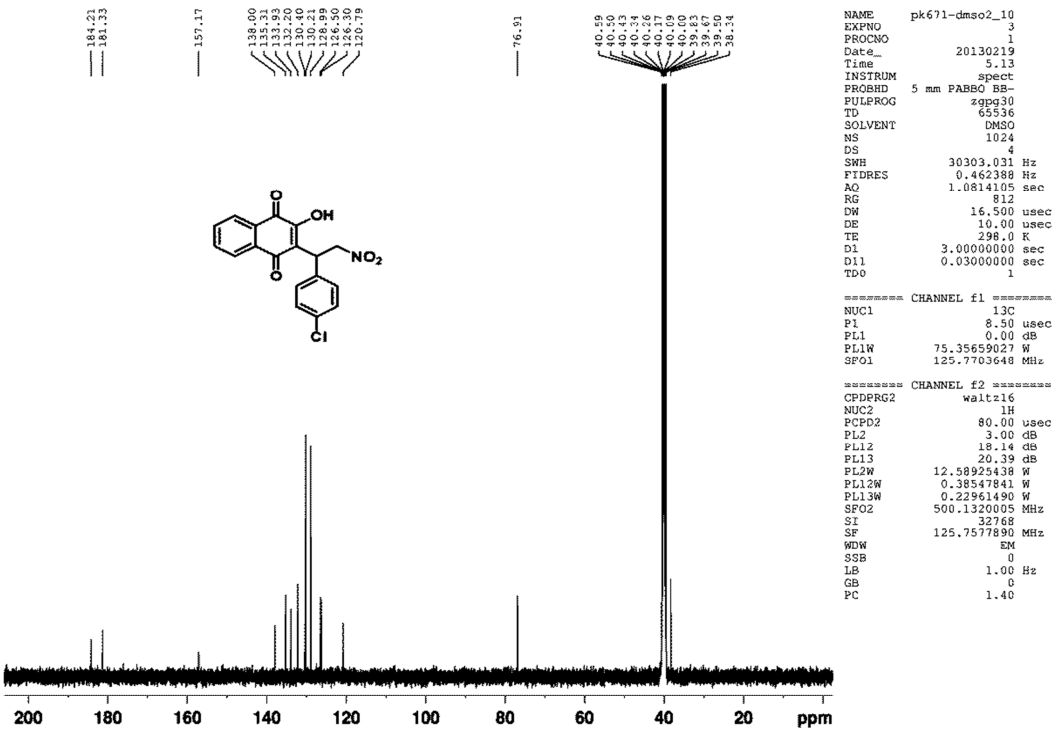


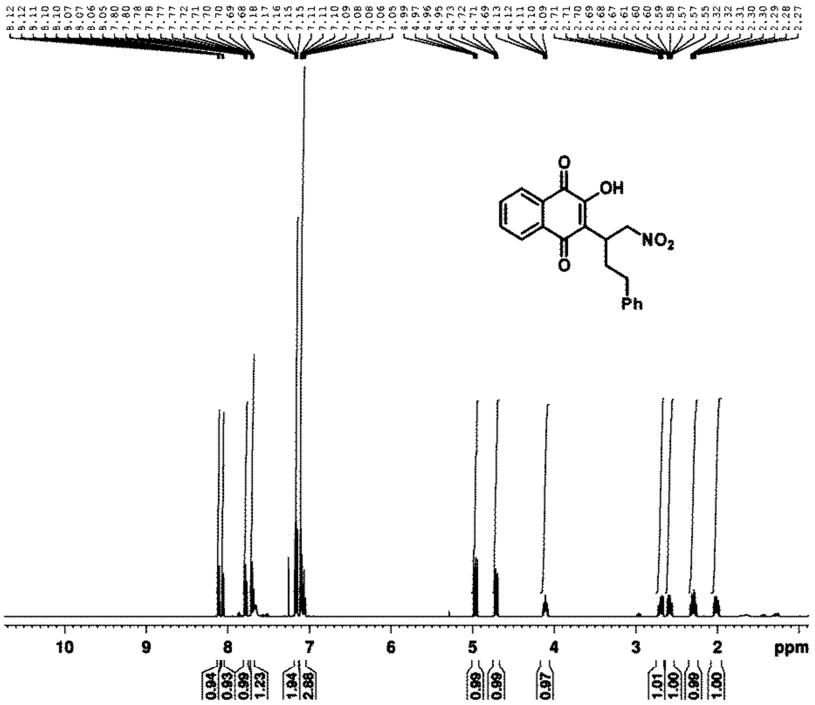
NAME	pk672p_10
EXPNO	1
PROCNO	1
Date_	20121203
Time	10.42
INSTRUM	FOURIER300
PROBHD	5 mm DUL 13C-1
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	8
DS	2
SWH	6103.516 Hz
FIDRES	0.093132 Hz
AQ	5.3687592 sec
RG	64.6737
DW	81.920 usec
DE	6.50 usec
TE	298.1 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
SFO1	300.1818011 MHz
NUC1	1H
P1	8.20 usec
SI	32768
SF	300.1800050 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.40



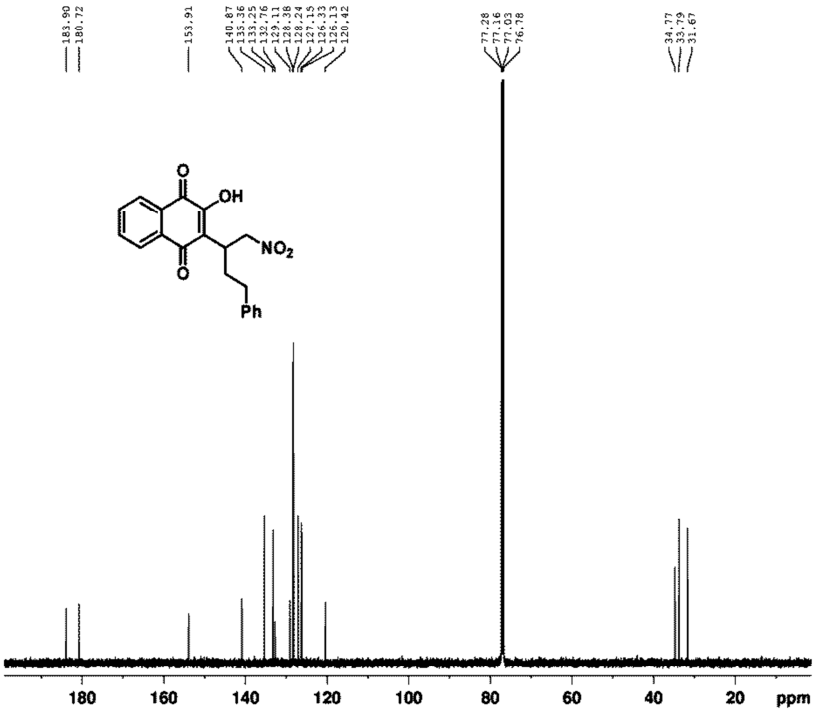
NAME	pk672pt_11
EXPNO	3
PROCNO	1
Date_	20130119
Time	1.45
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	30303.031 Hz
FIDRES	0.462388 Hz
AQ	1.0814105 sec
RG	812
DW	16.500 usec
DE	10.00 usec
TE	297.9 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	8.50 usec
PL1	0.00 dB
PL1W	75.35659027 W
SFO1	125.7703648 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	3.00 dB
PL12	18.14 dB
PL13	20.39 dB
PL2W	12.58925438 W
PL12W	0.38547841 W
PL13W	0.22961490 W
SFO2	500.1320005 MHz
SI	32768
SF	125.7577890 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



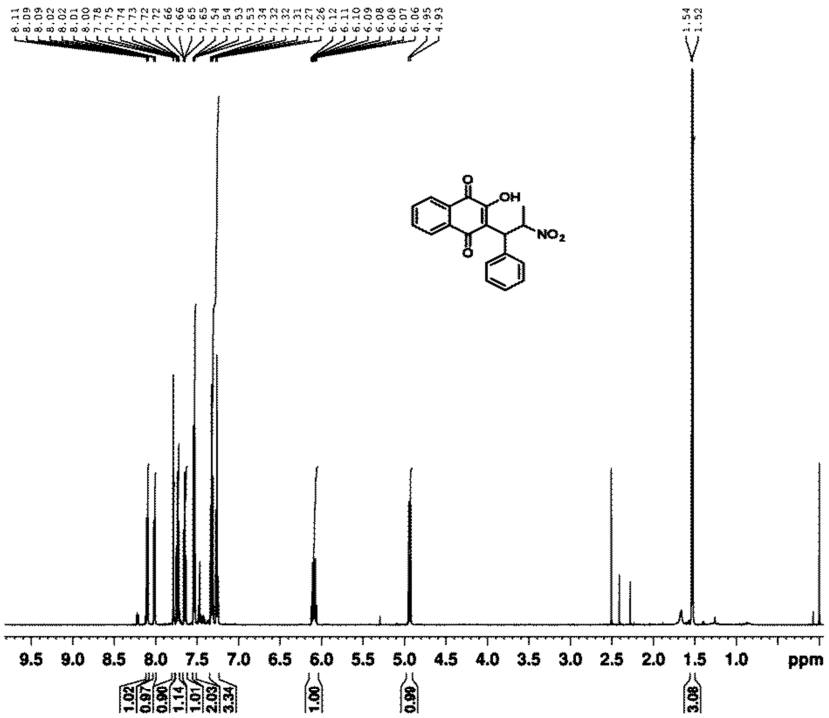




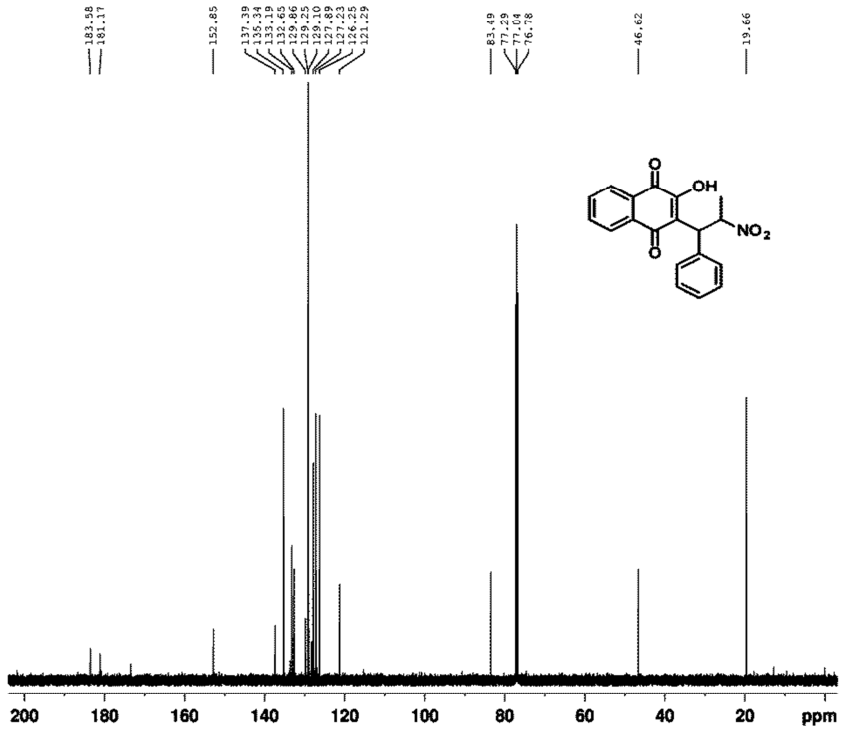
NAME	pk715t_10
EXPNO	1
PROCNO	1
Date_	20130222
Time	19.51
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	8
DS	2
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7264309 sec
RG	101
DW	83.200 usec
DE	10.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	1H
P1	13.80 usec
PL1	3.00 dB
PL1W	12.58925438 W
SFO1	500.1325007 MHz
SI	16384
SF	500.1300161 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00



NAME	pk715_11
EXPNO	1
PROCNO	1
Date_	20130220
Time	20.20
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	30303.031 Hz
FIDRES	0.462388 Hz
AQ	1.0814105 sec
RG	812
DW	16.500 usec
DE	10.00 usec
TE	298.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
======== CHANNEL f1 ========	
NUC1	13C
P1	8.50 usec
PL1	0.00 dB
PL1W	75.35659027 W
SFO1	125.7703648 MHz
======== CHANNEL f2 ========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	3.00 dB
PL12	18.14 dB
PL13	20.39 dB
PL2W	12.58925438 W
PL12W	0.38547841 W
PL13W	0.22961490 W
SFO2	500.1320005 MHz
SI	32768
SF	125.7577890 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40



NAME	pk682pt_10
EXPNO	2
PROCNO	1
Date_	20130118
Time	19.53
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	8
DS	2
SWH	6009.615 Hz
FIDRES	0.183399 Hz
AQ	2.7264309 sec
RG	228
DW	83.200 usec
DE	10.00 usec
TE	298.0 K
D1	1.00000000 sec
TD0	1
========== CHANNEL f1 ==========	
NUC1	1H
P1	13.80 usec
PL1	3.00 dB
PL1W	12.58925438 W
SFO1	500.1325007 MHz
SI	16384
SF	500.1300140 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

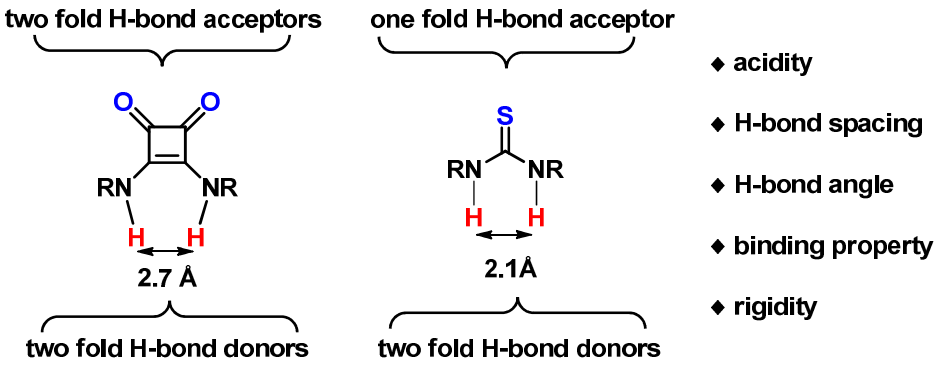


NAME	pk682pt_11
EXPNO	1
PROCNO	1
Date_	20130119
Time	2.12
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	512
DS	4
SWH	30303.031 Hz
FIDRES	0.462388 Hz
AQ	1.0814105 sec
RG	812
DW	16.500 usec
DE	10.00 usec
TE	298.0 K
D1	1.00000000 sec
D11	0.03000000 sec
TD0	1
========== CHANNEL f1 ==========	
NUC1	13C
P1	8.50 usec
PL1	0.00 dB
PL1W	75.35659027 W
SFO1	125.7703648 MHz
========== CHANNEL f2 ==========	
CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	3.00 dB
PL12	18.14 dB
PL13	20.39 dB
PL2W	12.58925438 W
PL12W	0.38547841 W
PL13W	0.22961490 W
SFO2	500.1320005 MHz
SI	32768
SF	125.7577890 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

4-II. POLYSTYRENE-SUPPORTED THIOUREA AND SQUARAMIDE ORGANOCATALYSTS

Hydrogen bonding organocatalysts are one of the main sub-groups of non-covalent catalysts, thioureas and squaramides being well-known members of this family. Both thioureas and squaramides have been used as organocatalysts for many years. The history of thioureas in asymmetric organocatalytic reactions is almost a decade older than squaramides. However, nowadays, both of them have been used extensively in various transformations.

As it has been discussed in previous chapters separately, thioureas (see Chapter 3) and squaramides (see Chapter 4.I) have different features depending on their nature. In short, they differ in acidity, binding property, H- bond spacing between the two N-H protons and rigidity in the structure (Scheme 4.5). In a field so sensitive to small changes as catalysis, these differences make them specific for different applications.



Scheme 4.5. H-bond acceptor and donor centers in squaramides and thioureas.

Due to their versatile use as H-bonding organocatalysts, the possibility of developing a heterogenized version of these catalysts attracted the interest of researchers. However, so far only a few studies have been done on the immobilization of H-bonding thioureas or squaramides.[16]

[16] a) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901-4902. b) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 1279-1281. c) Miyabe, H.; Tuchida, S.; Yamauchi, M.; Takemoto, Y. *Synthesis* **2006**, *19*, 3295-3300. d) Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, *5*, 779-790. e) Chuan, Y.; Chen, G.; Peng, Y. *Tetrahedron Lett.* **2009**, *50*, 3054-3058. f) Li, J.; Yang, G.; Qin, Y.; Yang, X.; Cui, Y. *Tetrahedron: Asymmetry* **2011**, *22*, 613-618. g) Fotaras, S.; Kokotos, C. G.; Kokotos, G. *Org. Biomol. Chem.* **2012**, *10*, 5613-5619. h) Fredriksen, K. A.; Kristensen, T. E.; Hansen, T. *Beilstein J. Org. Chem.* **2012**, *8*, 1126-1133. i) Kardos, G.; Soós, T. *Eur. J. Org. Chem.* **2013**, *21*, 4490-4494.

The first immobilized (thio)urea organocatalysts were used by Jacobsen *et al.* in the asymmetric Strecker reaction.[16a,b] The idea of immobilization was inspired by the Schiff base derivative, which belongs to an emerging class of catalysts and that was one of the most commonly supported ligands in the literature. The catalyst structure was modified with a diamine instead of an amino alcohol, in order to immobilize it onto a solid support. Thus, the second nitrogen atom placed on the chiral backbone was used for attachment (Figure 4.5). After parallel catalyst library screening they found that $linker_1$ was responsible for the lower enantioselectivity and in the optimized catalyst structure they preferred direct immobilization from the amino acid group to the polystyrene support. The crucial moieties responsible for high enantioselectivity were found to be the bulky substituents at both the amino acid position and at the 3-position of the salicylimine moiety. By changing the substituents on the catalyst, they found a superior structure and completed the scope of the Strecker reaction with high yield and enantioselectivities. At the same time, they reported that the catalyst could be recycled unlimitedly without loss of either activity or enantioselectivity.

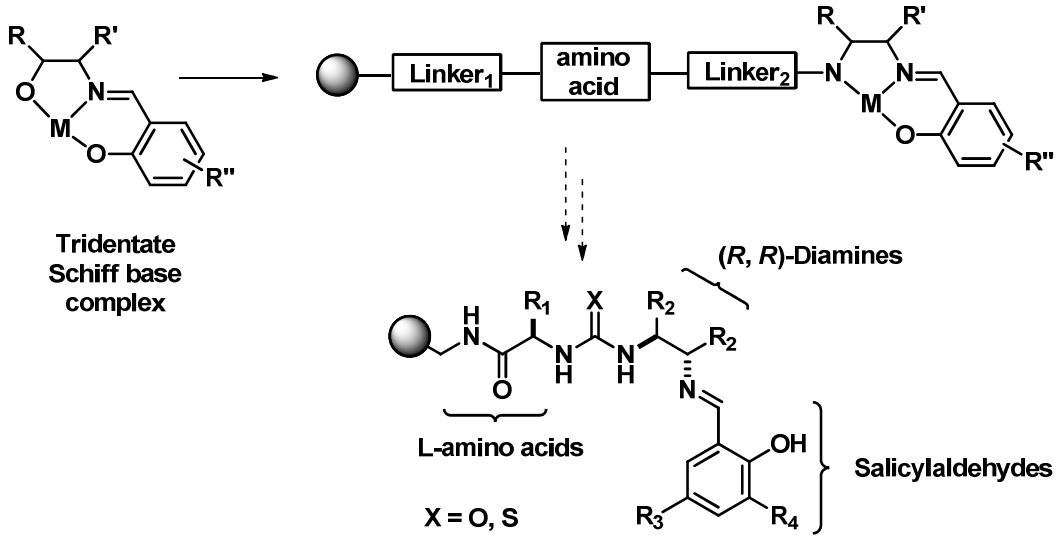
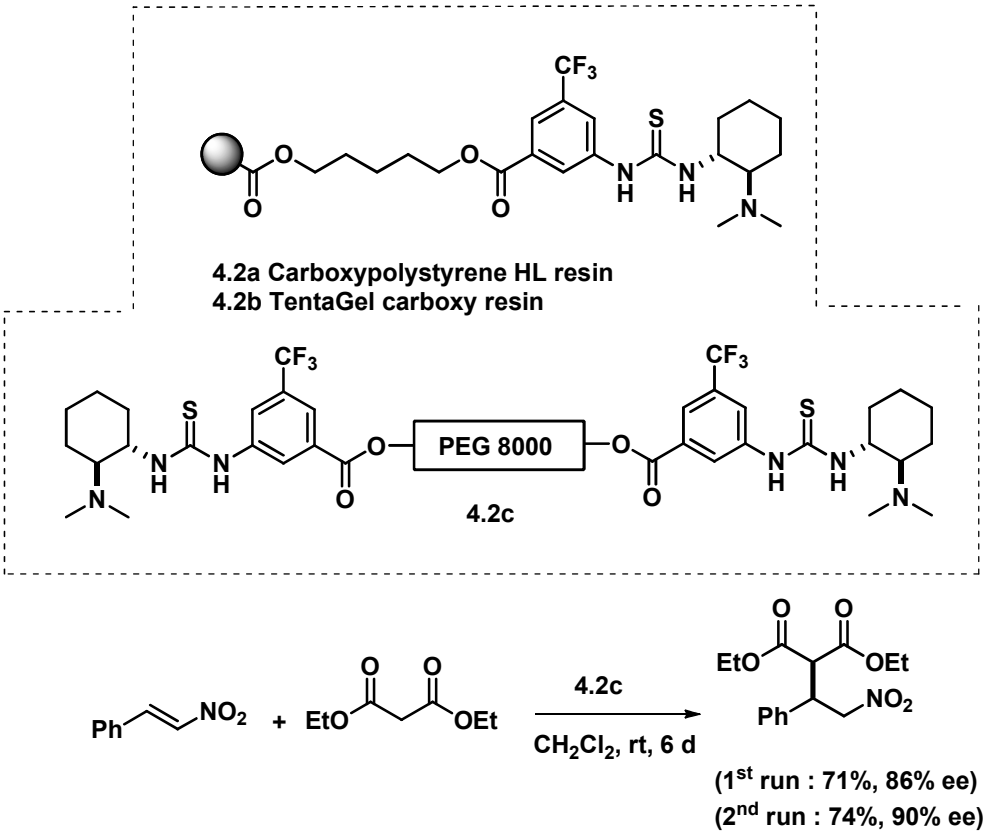


Figure 4.5. Concept for the immobilization of Jacobsen groups (thio)urea catalysts onto polystyrene.

In 2006, the Takemoto group published a study on the immobilization of a chiral thiourea onto a polymer support.[16c] Carboxypolystyrene HL resin-bound, TentaGel carboxy resin-bound and also PEG-bound thioures were developed to be evaluated in the Michael and tandem Michael reactions of *trans*-β-nitrostyrene. Their supporting strategy was designed to use an ester moiety to attach the

thiourea functionality to several polymer supports. At first, cross-linked polystyrenes were used as support and pentane-1,5-diol was used as a spacer (Scheme 4.6). However, both catalysts showed lower activity when compared to the soluble homogeneous catalyst. Then, they decided to use a non-crosslinked polymer as the support for immobilization, and a soluble PEG-bound thiourea was prepared. The catalytic activity of the catalyst was tested in the same malonate addition to *trans*-β-nitrostyrene reaction and it was found that with the PEG-bound thiourea (**4.2c** in Scheme 4.6) the reaction rate decreased but the enantioselectivity was good. The catalyst could also be recycled a couple of times without decrease in yield and enantioselectivity.



Scheme 4.6. Takemoto's polymer-supported thiourea catalysts.

After that, only a few more studies have been published with supported thiourea organocatalysts. One of them was from Schreiner *et al.,* where polystyrene bound thioureas were used in the tetrahydropyran and 2-methoxypropene protection of alcohols, phenols and other ROH derivatives.[16d] High catalytic efficiency and remarkable turnover numbers were achieved with only 0.001 mol% catalyst loadings. The other example was from Peng *et al.*, who used insoluble, non-swelling MPS-supported (mesoporous polymer) thiourea

organocatalysts in the Michael addition of ketones to nitrostyrenes in water.[16e] More recently, the Hansen group has used polymer supported *Cinchona* derived thiourea organocatalysts obtained by the thiol-ene suspension copolymerization of polyfunctional thiols and alkenes together.[16h] However, the catalyst showed poor recycling ability, which was explained in terms of the low functionalization and free thiol groups on the polymer.

On the other hand, for immobilized squaramide organocatalysts there is only one example published so far, which has been already mentioned in Chapter 4-I. There in, Soós *et al.* have reported the use of aminomethyl-functionalized macroporous and microporous polystyrene supported squaramides.[15] A chart with the polymer supported thioureas and squaramides can be found in Figure 4.6.

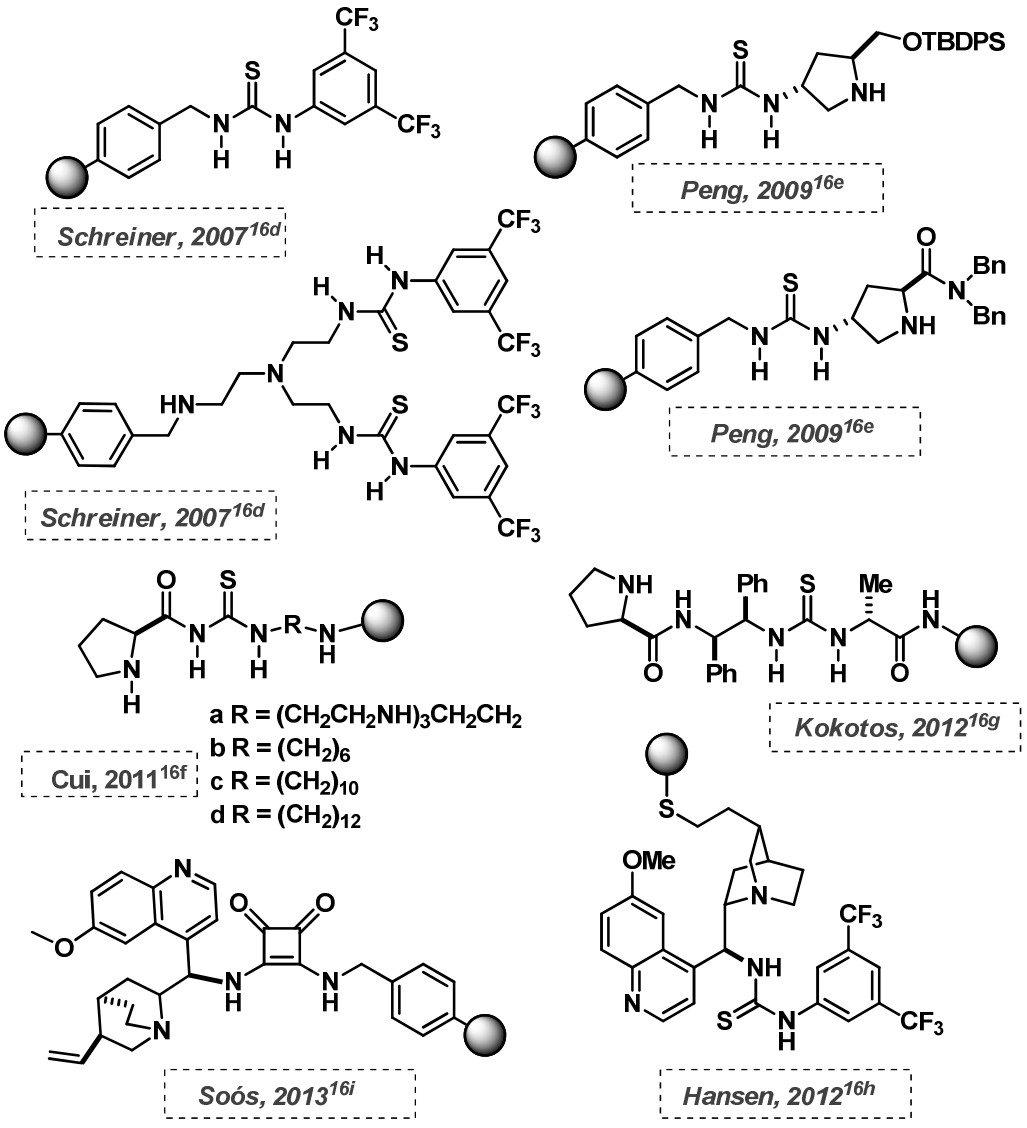
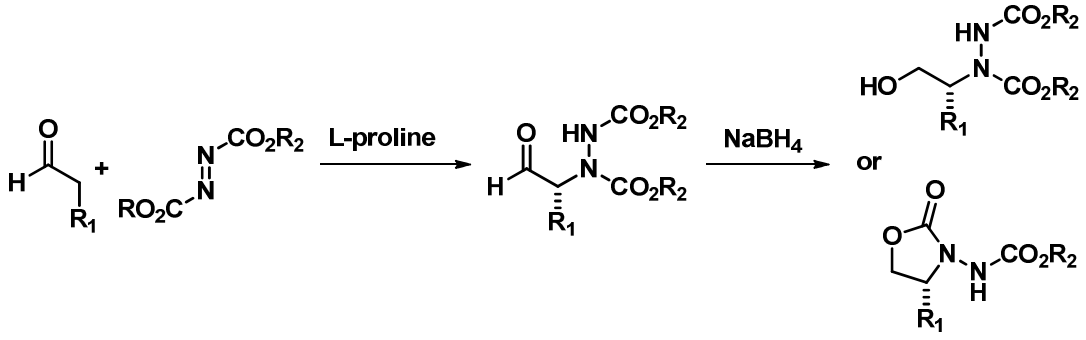


Figure 4.6. Examples of polymer supported thioureas and squaramide in literature.

Although, organocatalysis was introduced more than a decade ago, it still suffers from disadvantages such as the requirement of high cost for the synthesis of the catalysts, high catalyst loading, and time-consuming processes needed for the separation of catalytic species. To solve these problems, the uses of recoverable and recyclable supported catalysts are attractive solutions. For this reason, by using in the information in the literature and our previous experience, we wanted to apply our squaramide immobilization strategy to the thiourea analogues. As the remarkable catalytic activity and robustness of our immobilized squaramide organocatalyst in Michael addition reactions was previously shown (see Chapter 4-I), we decided to try and compare both catalysts in C–N bond forming α-amination reactions.

4.2. Enantioselective α-Amination Reactions Catalyzed by Thiourea and Squaramide Organocatalysts

The organocatalytic reaction, in which nitrogen atom is directly introduced into the α-position of an activated carbonyl group, was selected due to the fact that it represents a powerful methodology for the synthesis of optically active α-amino aldehydes, α-amino alcohols, and α-amino acids, which are important intermediates in many natural products. The first organocatalytic direct α-amination reaction was independently reported in 2002 by the groups of List and Jørgensen.[17] They demonstrated that L-proline efficiently catalyzes the asymmetric α-amination of aldehydes with azodicarboxylates (Scheme 4.7). Due to the unstable nature of the formed product, it had to be in situ reduced to the corresponding amino alcohol or cyclized under basic conditions.



Scheme 4.7. Proline-catalyzed α-amination of aldehydes.

[17] a) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1790-1793. b) List, B. *J. Am. Chem. Soc*. **2002**, *124*, 5656-5657.

Later on, Jørgensen and co-workers also reported the proline-catalyzed enantioselective direct α-amination of ketones, which also took place with excellent enantioselectivities.[18] After that, many other proline derived catalysts have been used in α-amination reactions efficiently. In addition to proline-derived catalysts, cinchona alkaloids,[19] chiral (thio)ureas,[20] guanidines[21] and chiral phase transfer catalysts[22] have also been used with success (Figure 4.7).

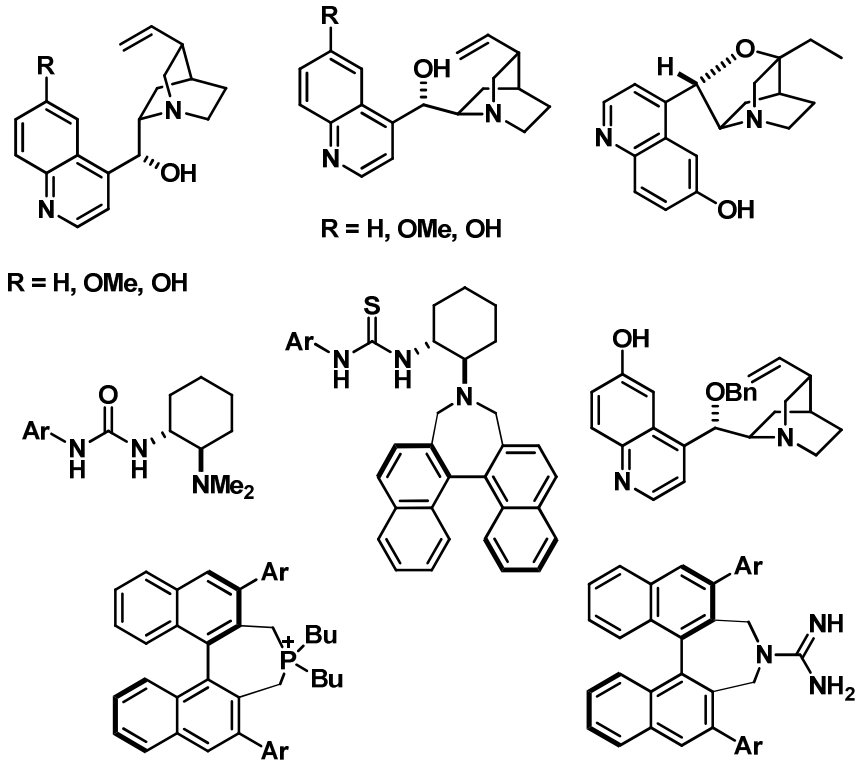
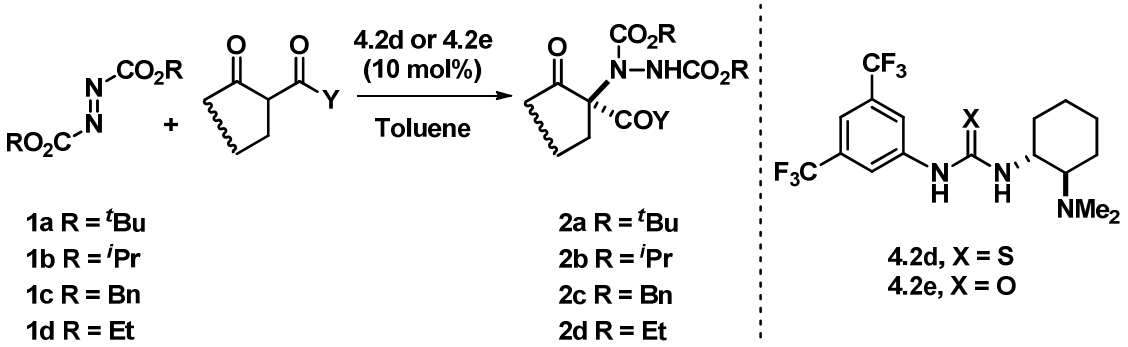


Figure 4.7. Examples of catalysts used in the α-amination reaction in the literature.

The first (thio)urea organocatalyzed α-amination reaction was reported by Takemoto *et al.*, in 2006.[20a] They described the enantioselective hydrazination of 1,3-dicarbonyl compounds with tertiary amino bearing (thio)urea catalysts. Even

[18] Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2002**, *124*, 6254-6255.
[19] a) Pihko, P. M.; Pohjakallio, A. *Synlett* **2004**, *12*, 2115-2118. b) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120-8121 c) Liu, X.; Li, H.; Deng, L. *Org. Lett.* **2005**, *7*, 167-169.
[20] a) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, *1*, 137-140. b) Kim, S. M.; Lee, J. H.; Kim, D. Y. *Synlett* **2008**, *17*, 2659-2662. c) Jung, S. H.; Kim, D. Y. *Tetrahedron Lett.* **2008**, *49*, 5527-5530. d) Inokuma, T.; Furukawa, M.; Uno, T.; Suzuki, Y.; Yoshida, K.; Yano, Y.; Matsuzaki, K.; Takemoto, Y. *Chem. Eur. J.* **2011**, *17*, 10470-10477. e) Zhou, F.; Ding, M.; Liu, Y. L.; Wang, C. H.; Ji, C. B.; Zhang, Y. Y.; Zhoua, J. *Adv. Synth. Catal*. **2011**, *353*, 2945-2952.
[21] a) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc*. **2006**, *128*, 16044-16045. b) Terada, M.; Amagai, K.; Ando, K.; Kwon, E.; Ube, H. *Chem. Eur. J*. **2011**, *17*, 9037-904. c) Simón, L.; Goodman, J. M. *J. Am. Chem. Soc*. **2012**, *134*, 16869-16876.
[22] He, R.; Wang, X.; Hashimoto, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 9466-9468.

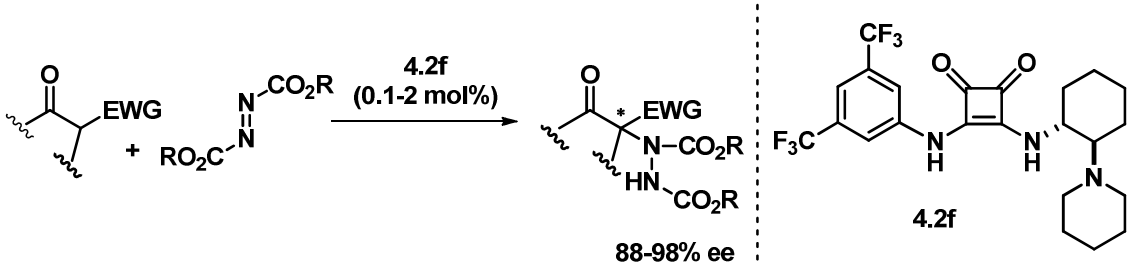
though thiourea, has been found to be superior catalyst, in terms of enantioselectivity, a urea catalyst was used for the scope of the reaction due to the slow decomposition of the thiourea under reaction conditions. After the optimization of reaction conditions, the α-hydrazination reaction of β-keto esters and 1,3-diketones proceeded in high yields and enantioselectivities (up to 91%) by using a bifunctional urea catalyst (Scheme 4.8).



Scheme 4.8. Hydrazination of 1,3-dicarbonyl compounds with azodicarboxylates in the presence of catalysts **4.2d** and **4.2e**.

Another remarkable example of direct amination with thiourea organocatalysts was done by Kim *et al.*[20b] involving the treatments of α-cyanoketones with azodicarboxylates in the presence of a chiral thiourea with a bulky and rigid binaphthyl scaffold. The α-aminated α-cyanoketones were obtained with excellent enantiomeric excesses. In addition to thioureas, squaramides also proved successful organocatalysts in the α-amination reaction. The squaramide organocatalyst possessing the (*R*,*R*)-1,2-diaminocyclohexane moiety was used in the enantioselective α-hydrazination of 1,3-dicarbonyl compounds by Rawal *et al.* (Scheme 4.9). Outstanding results were obtained with catalyst **4.2f** at room temperature and even with low catalyst loadings (0.1 mol%) no significant deterioration of enantioselectivity was reported. The α-amination products were obtained under mild reaction conditions and shorter reaction times with this squaramide organocatalyst.[23]

[23] Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.*, **2010**, *12*, 2028-2031.



Scheme 4.9. α-Amination of 1,3-dicarbonyl compounds with squaramide organocatalyst **4.2f**.

4.3. AIM OF OUR STUDY

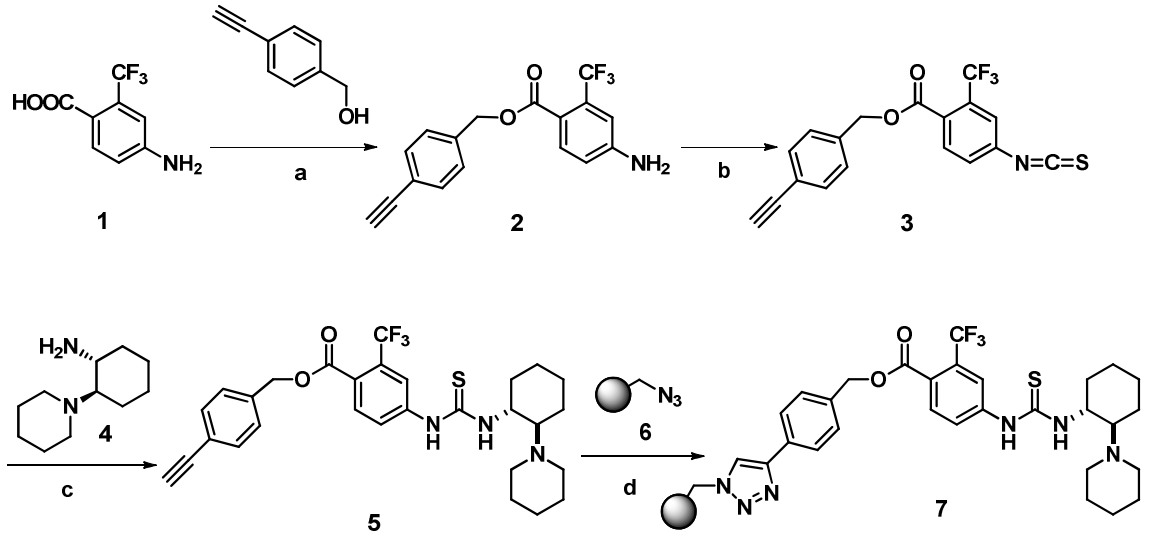
As mentioned earlier in the chapter, we wanted to prepare immobilized thiourea organocatalysts to complement the supported squaramides and compare the catalytic efficiency of each catalysts in the C–N bond forming α-amination reaction of 1,3-dicarbonyl compounds.

4.4. RESULTS AND DISCUSSION

4.4.1. Polystyrene Supported Thiourea Organocatalyst

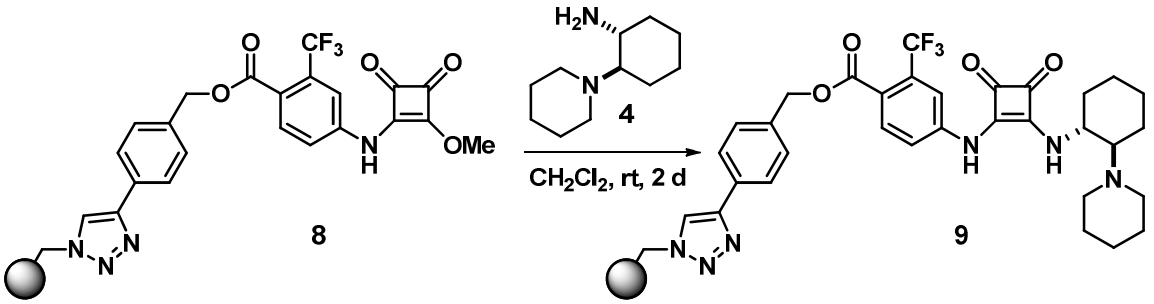
Preparation

In order to prepare our target PS-supported thiourea organocatalyst, we followed the same procedure previously developed for the synthesis of the PS-supported squaramide. The carboxy group of molecule **1** was the connecting unit for immobilization purposes, and it was placed in the *para* position with respect to the amino group to maximize the spatial separation with the active part of the catalyst. Esterification of **1** with acetylenic alcohol led to ester **2**. Then, the intermediate **2** was treated with thiophosgene under biphasic conditions to form an isothiocyanate intermediate **3** in quantitative yields without purification. The next step was the reaction of **3** with chiral amine **4** to complete the synthesis of the homogeneous thiourea **5**. The last step was the immobilization of this intermediate **5** onto azidomethylpolystyrene **6** via CuAAC reaction (Scheme 4.10).



Scheme 4.10. Synthesis of catalyst **7**: a) DCC, DMAP, CH_2Cl_2, rt, 2 d, 90% b) $CSCl_2$, CH_2Cl_2, $NaHCO_3$, 0 ºC, 1 h, quantitative c) **4**, CH_2Cl_2, rt, overnight, 96% d) CuI, DIPEA, THF-DMF, 40 ºC, 4 d, 91%.

The related synthesis of the PS-supported squaramide organocatalyst has been already detailed in chapter 3-I, but that approach had to be adapted in the final part for PS-supported thiourea. The difference lies in the fact that, in the previous case, an intermediate **8** was already supported onto polystyrene, and the chiral amine **4** was added in the last step (Scheme 4.11). It is to be noted that this second approach offers the additional advantage of its modular character. Thus, a variety of supported squaramides could be readily prepared from **8** by simply changing the nature of the primary amine used in the last synthetic step.



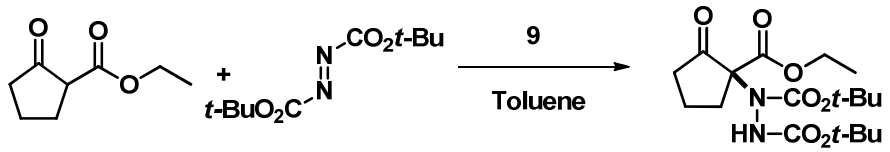
Scheme 4.11. Last step of the PS-supported squaramide organocatalyst synthesis.

Optimization and Screening

To test the efficiency of the catalysts, we decided to try the addition of ethyl 2-oxocyclopentanecarboxylate to di-*tert*-butyl azodicarboxylate. First, the reaction was tested with catalyst **9** to optimize the conditions. Then, the effect of catalyst

loading, temperature, concentration and inert atmosphere were tested. According to the preliminary results, with 2 mol% catalyst loading the α-amination product was obtained with very high yields and good enantioselectivities in short times (Table 4.1, entry 1).

Table. 4.1. Screening of the conditions for the α-amination reactions **10** with **11**.



10a **11a** **12**

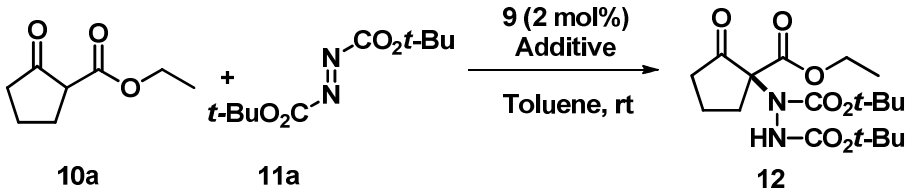
Entry	Catalyst Loading (mol%)	Time (h)	T (°C)	Conc. (M)	Yield (%)	ee (%)
1	2	2	rt	0.7	96	86
2	1	3.5	rt	0.7	96	82
3	2	5	0	0.7	92	73
4	2	2	rt	0.35	90	72
5	2	3	rt	0.7	93	84

Reducing the catalyst loading (Table 4.1, entry 2) only doubled up the reaction time. The temperature change (Table 4.1, entry 3) also affected the reaction time, but the enantioselectivity was also lowered due to the poor swelling ability of polymers at low temperatures. Changing the concentration (Table 4.1, entry 4) and performing the reaction under inert conditions (Table 4.1, entry 5) did not improve the results any further.

In a second stage, we decided to try some additives, to achieve higher enantioselectivities. First, molecular sieves, magnesium sulfate and sodium sulfate were tested as drying agents to observe the effect of moisture. The highest enantioselectivity was achieved with $MgSO_4$, while the other additives did not show any effect. Therefore, we thought that the results obtained with $MgSO_4$ can be related with its Lewis acidic nature. Also, a background reaction was performed with only 10 mol% $MgSO_4$, very low conversion being observed after 6 h (Table 4.2, entry 7). When lithium perchlorate and lithium chloride were used as an additive, the reactions were completed in very short time, but very low

enantioselectivities were recorded due to the concomitant acceleration of the background reaction (Table 4.2, entries 4-5).

Table 4.2. Additive screening in the reaction of **10** with **11**.



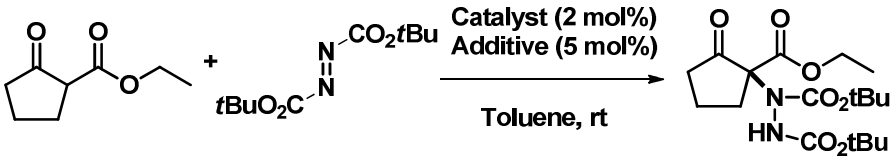
10a 11a 12

Entry	Time (h)	Additive (5 mol%)	Conv.(%)	ee (%)
1	2	4 Å MS	99	86
2	4	$MgSO_4$	99	93
3	2.5	Na_2SO_4	99	81
4	0.25	$LiClO_4$	99	23
5	0.5	LiCl	99	48
6	4.5	$Mg(ClO_4)_2$	99	89
7[a]	6	$MgSO_4$	6	-

[a] Background reaction only with 10 mol% $MgSO_4$.

Although the effects of LA on the enantioselectivity of the reaction could not be fully rationalized, we decided to further screen the effect of these additives. All the other Lewis acids tested gave competing reactions except $MgSO_4$. The effect of $MgSO_4$ in squaramide catalyzed reaction looks like unique due to its dual binding ability. After all, addition to squaramide catalyst **9**, PS-supported thiourea organocatalyst tested in same reaction with and without using $MgSO_4$ additive, the results showed that using $MgSO_4$ did not alter either the activity or the enantioselectivity (Table 4.3, entries 6-7).

Table 4.3. Lewis acid screening in the reaction of **10** with **11**.



10a **11a** **12**

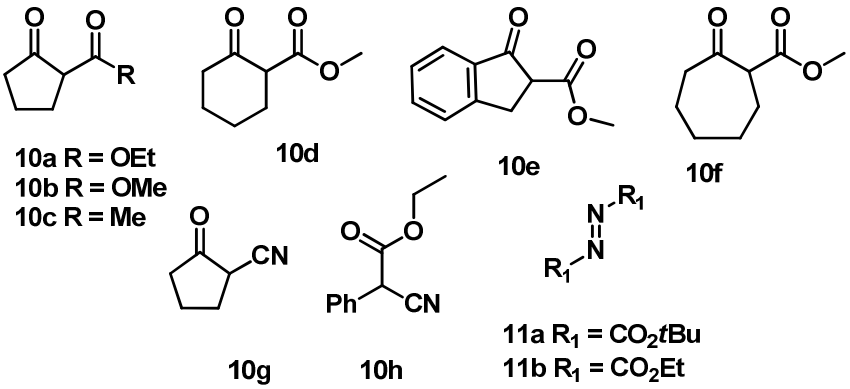
Entry	Catalyst	Additive	Time (h)	Conv.(%)	ee %
1	**9**	$MgSO_4$	4	99	93
2	**9**	CuOTf	24	99	12
3	**9**	$Mg(OTf)_2$	24	99	56
4	**9**	$La(OTf)_3$	1,5	99	14
5	**9**	$Eu(OTf)_3$	2	99	13
6[b]	**7**	-	4	99	89
7[b]	**7**	$MgSO_4$	4	99	89

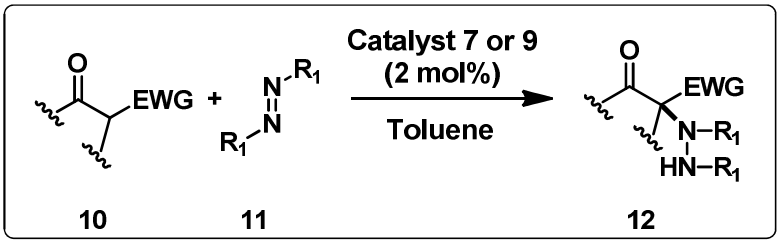
[a] Reactions performed in glove box.

[b] Reactions performed under ambient conditions.

To compare the activity of the catalysts, the reactions aiming at determining the scope of study were performed with both the thiourea and the squaramide derivate. In the reactions catalyzed by squaramide **9**, $MgSO_4$ was used as an additive and, even though it is known that polymers work poorly below 0 ºC, some substrates were tested at low temperatures in an attempt to improve the enantioselectivity of the reaction. In some cases, diethyl azodicarboxylate was used in order to test the effect of the hydrazination reagent. When we analyze the results in Table 4.4, it can be seen that for five-membered ring substrates (entries 1-2) at the scope table very high yields and enantioselectivities were obtained with both catalysts at room temperature. The reaction of six membered ring substrates; in turn; (Table 4.4, entries 3- 4) did not give any product, which is probably due to steric reasons.

Table 4.4. Substrate scope with catalyst **7** and **9**.



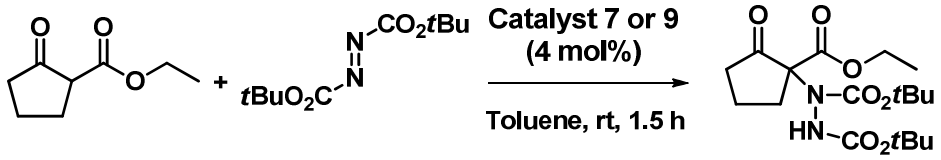


Entry	Substrate	R_1	Time (h)		Temp (ºC)		Yield (%)		ee (%)	
			9	***7***	***9***	***7***	***9***	***7***	***9***	***7***
1	**10a**	**11a**	4	4	rt	rt	92	95	93	92
2	**10b**	**11a**	4	4	rt	rt	94	90	96	93
3	**10d**	**11a**	24	24	rt	rt	nr	nr	-	-
4	**10d**	**11b**	24	24	0	0	nr	nr	-	-
5	**10e**	**11a**	24	0.75	–40	0	nr	92	-	80
6	**10e**	**11b**	0.5	-	rt	-	94	-	48	-
7	**10c**	**11a**	24	2h	rt	–20	91	89	72	66
8	**10c**	**11b**	1.5	0.75	–20	rt	93	93	88	66
9	**10f**	**11a**	24	30	rt	rt	42	71	85	80
10	**10g**	**11a**	24	24	rt	rt	37	43	25	29
11	**10h**	**11a**	3.5	-	0	-	89	-	10	-
12	**10h**	**11b**	5min	-	0	-	94	-	10	-

[a] Reactions with catalyst **9** performed with 5 mol% $MgSO_4$ as additive.

For the indanone containing substrate **10e**, if the reaction was performed at room temperature or at 0 ºC, the product was obtained in very short time albeit with low enantioselectivity. Not unexpectedly, when the temperature was lowered to –40 ºC, no product was obtained (Table 4.4, entry 5, 6). Reactions of other substrates also gave good yields but with poor enantioselectivities compared to homogeneous analogues.[23] Then, we decided to perform a recycling experiment with the substrates that gave high yield and enantioselectivity. In the recycling experiments, 4 mol% catalyst loading was used, and in the case of PS-supported squaramide **9**, 10 mol% $MgSO_4$ was added in addition to the catalyst at the beginning of the reaction. The catalyst with $MgSO_4$ could be recycled for 5 runs and after each cycle, a decrease in yield and enantioselectivity was observed. Similar results were observed with the PS-supported thiourea catalyst **7**, which was used without any additive. While the yields decreased, the enantioselectivities remained higher than in the case of catalyst **9**.

Table 4.5. Recycling experiments of catalyst **7** and **9**.



Cycle #	Yield %		ee %	
	9[a]	***7***	***9***[a]	***7***
1	96	91	95	92
2	86	86	88	91
3	76	79	87	86
4	68	76	88	83
5	60	67	67	87

[a] Recycling of catalyst **9** done with $MgSO_4$ (10 mol%).

Afterwards, PS-supported thiourea organocatalyst **7** was found to be a good candidate for evaluation in continuous flow applications. In order to start a new process higher amount of catalyst were needed and new batches of PS-supported thiourea catalysts were synthesized following different routes (Figure 4.8) to eliminate problems arising from presumably copper contamination in the last step of the initial route. In the old synthetic method, the homogeneous thiourea was

formed in two steps starting from the linker-NH_2 molecule and then it was immobilized to the polymer by means of a CuAAC reaction by using CuI and DIPEA. In this last step, high amounts of CuI were needed for the click reaction. We speculated that the copper could coordinate to the thiourea and block the active site of the catalyst. To circumvent this difficulty, we decided to change to route B. In this approach, the click reaction was performed in first step with the linker-NH_2 molecule without any problem, and the isothiocyanate was prepared from the chiral amine (chiral NCS in Figure 4.8). Then, they were reacted to form the PS-supported thiourea catalyst. Although the catalyst was obtained with moderate loading, when catalyst **7** prepared by this route was tested in the model α-amination reaction, it showed very low activity.

In route C, the isothiocyanate was prepared from the linker-NH_2, and then this intermediate was immobilized via click chemistry onto the polymer. However, following the click reaction by IR was not easy and the polymer was obtained with low functionalization. Then, the final step was the reaction of this low functionalized polymer with the chiral amine. In the end, the catalyst obtained with route C did not showed neither high activity nor enantioselectivity.

As a last possibility we attempted route D, in which the click reaction was performed with the linker-NH_2 molecule again and then the isothiocyanate functional group was directly prepared on the polymer. The last step involved the reaction of this isothiocyanate polymer with the chiral amine to form the PS-supported thiourea **7**. Although, the catalyst obtained by following route D has the highest functionalization in the whole series, it again showed low activity and enantioselectivity compared to the initial PS-supported thiourea organocatalyst. On the other hand, the catalyst obtained with route D gave better results compared to route B and C; in this case, the low activity of the catalyst might be due to the high level of functionalization. In supported catalysts, the optimal loading amount is an important issue: if this value is in the upper limit, again, catalysts can show low catalytic activity due to the limited accessibility of the active sites or undesired interactions with each other.

After all, trying different routes did not help to improve catalyst efficiency, and the new batches of PS-supported thiourea organocatalyst **7** synthesized with route A did not give reproducible results. For further studies, the supporting

strategy can be changed. Instead of azidomethylpolystyrene, other Merrifield resin derivatives can be used, and copper-free coupling reactions can be tried for the immobilization.

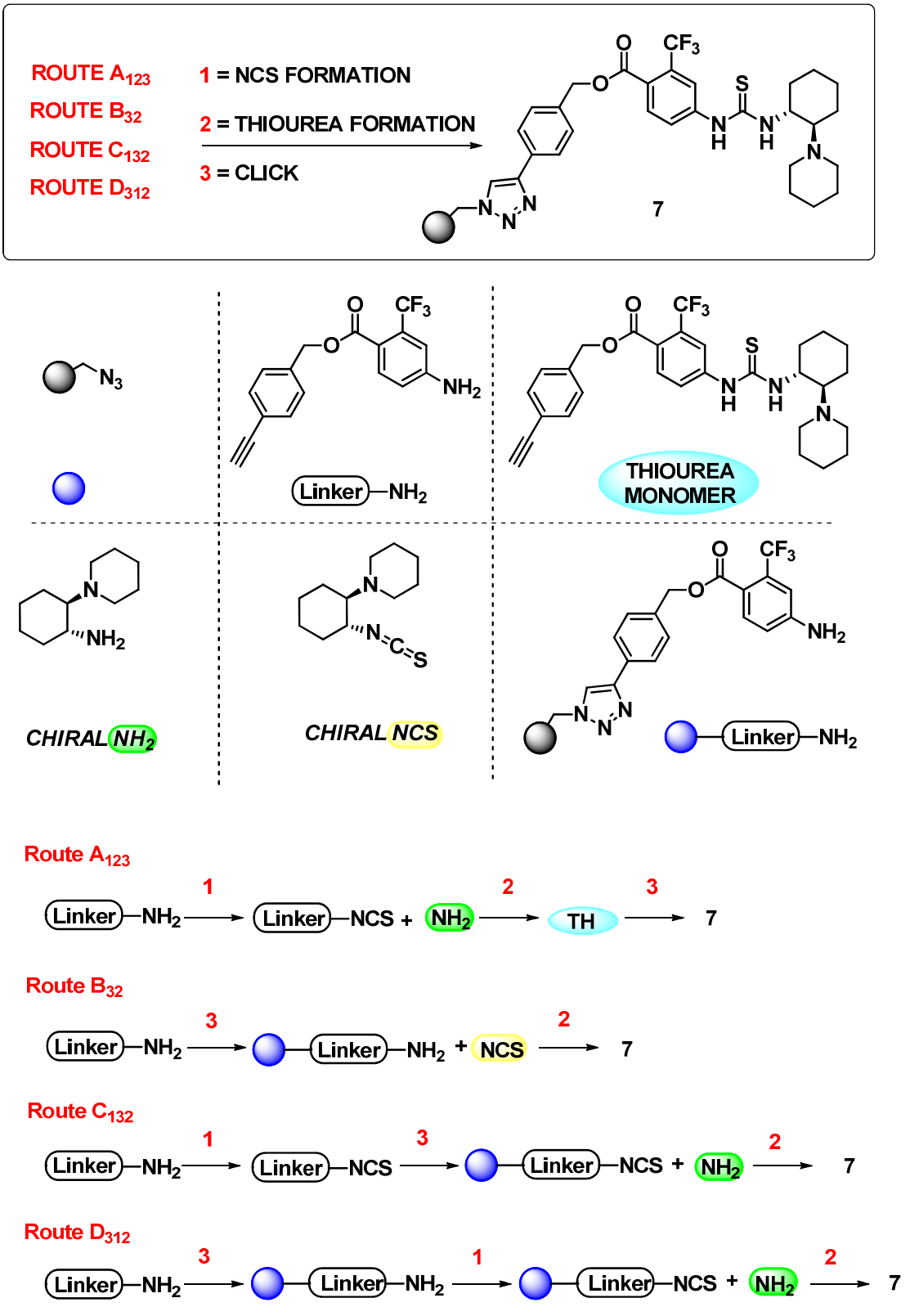


Figure 4.8. Routes followed for the synthesis of the PS-supported thiourea organocatalyst **7**.

4.5. CONCLUSION

In this chapter, we aimed to design a simple and general pathway for the synthesis of both PS-supported squaramide and thiourea organocatalysts. In the synthesis of PS-supported squaramide, the approach we followed succeeded and a general pathway could be designed for the synthesis of such organocatalyst derivatives. In the case of PS-supported thioureas, the obtained results showed poor reproducibility which means that further modifications are still required for immobilization. This can be done either by changing the functional group on the polymer or on the monomer. The activity of our PS-supported catalyst in the α-amination reactions was good; however, enantioselectivities were moderate at room temperature. To obtain higher selectivity, lower temperatures were necessary and in literature most of the reactions are done at very low temperatures.[20] However, we cannot work at these temperatures due to the poor swelling ability of polymers.

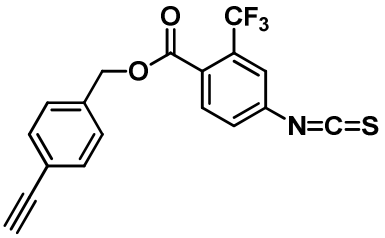
4.6. EXPERIMENTAL SECTION

General Methods and Materials

Unless otherwise stated, all reactions were conducted without exclusion of air or moisture. Synthesis grade solvents and reactants were used as received. All flash chromatographies were carried out using 60 mesh silica gel and dry-packed columns. NMR spectra were recorded at 400 MHz and 500 MHz for ^{1}H or at 100 MHz and 125 MHz for ^{13}C, respectively. ^{1}H NMR spectroscopy chemical shifts are quoted in ppm relative to internal tetramethylsilane (TMS) and ^{13}C NMR spectra to $CDCl_3$. FAB mass spectra were obtained on a Fisons V6-Quattro instrument, ESI mass spectra were obtained on a Waters LCT Premier Instrument and CI and EI spectra were obtained on a Waters GCT spectrometer. Specific optical rotation measurements were carried out on a Jasco P-1030 polarimeter equipped with a PMT detector using the Sodium line at 589 nm. High performance liquid chromatography (HPLC) was performed on Agilent Technologies chromatographs (Series 1100 and 1200), using Chiralcel AD-H and IC guard columns as noted. For the synthesis of PS-supported squaramide organocatalyst **9** and the intermediate **2** used in the synthesis of PS-supported thioure organocatalyst (Scheme 4.11) see

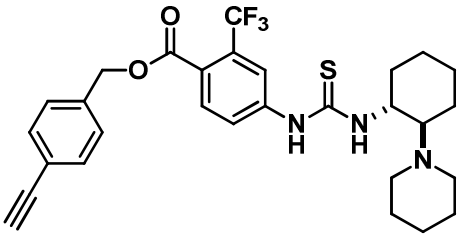
chapter 4-I supporting info. Chiral amine **4** was synthesized according to reported procedures.[11]

Synthesis of PS-Supported Thiourea Organocatalyst



4-ethynylbenzyl 4-isothiocyanato-2-(trifluoromethyl)benzoate (3)

A saturated solution of aqueous sodium bicarbonate (25 mL) was added to a solution of 4-ethynylbenzyl-4-amino-2-(trifluoromethyl)benzoate (3.8 mmol, 1.2 g) in dichloromethane (25 mL) at 0 °C. The mixture was stirred for 10 minutes, then stirring was stopped, and thiophosgene (4.0 mmol, 455 µL) was added to the dichloromethane (lower) layer in one portion via syringe. The resulting mixture was stirred (~500 rpm) for 1 h at 0 °C. The reaction was then transferred to a separatory funnel and the organic layer was removed. The aqueous phase was extracted with dichloromethane (3 x 50 mL) and the combined organics were dried over Na_2SO_4. Volatiles were removed under reduced pressure and the product was used in the next step without any further purification.



4-ethynylbenzyl 4-(3-((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)thioureido)-2-(trifluoro-methyl)benzoate (5)

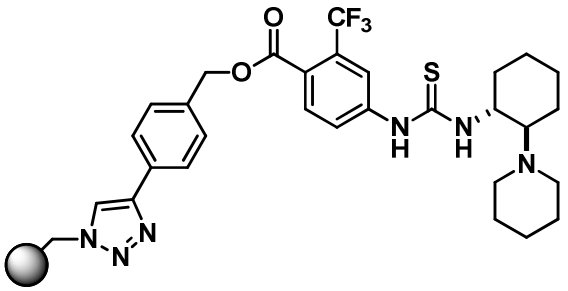
4-ethynylbenzyl-4-isothiocyanato-2-(trifluoromethyl)benzoate **3** (1.4 mmol, 0.5 g) was added to a solution of (1*R*,2*R*)-2-(piperidin-1-yl)cyclohexanamine (1.4 mmol, 0.25 g) in CH_2Cl_2 (6 mL) at room temperature. The resulting solution was stirred at room temperature overnight, and then the reaction mixture was concentrated under reduced pressure. The resulting residue was loaded onto a silica gel column

and purified by flash column chromatography using CH_2Cl_2 to CH_2Cl_2/MeOH (95:5) as eluent. The product was obtained as a white foam in 78% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85-7.80 (m, 3H), 7.49 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.30 Hz, 2H), 5.34 (s, 2H), 4.07 (br s, 1H), 3.10 (s, 1H), 2.81-2.77 (m, 2H), 2.69-2.61 (m, 2H), 2.53-2.47 (m, 2H), 1.99-1.85 (m, 2H), 1.77-1.71 (m, 1H), 1.68-1.47 (m, 4H), 1.46-1.40 (m, 2H), 1.36-1.13 (m, 5H).

^{13}C NMR (125 MHz, CH_3OD): δ 180.2, 165.7, 143.0, 136.3, (131.8 x 2), 131.4, 129.2 (q, J = 32.3 Hz), (128.1 x 2), 124.7, 123.9, 123.2 (q, J = 273.0 Hz), 122.4, 119.7, 82.6, 77.8, 67.9, 66.6, 32.1, 26.1, 24.7, 24.6, 24.3, 23.4.

HRMS (ESI+): *m/z* = 544.2240, calcd. for $C_{29}H_{33}F_3N_3O_2S$ $[M+H]^+$, found 544.2238.



4-(1H-1,2,3-triazol-4-yl)benzyl 4-(3-((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)-thioureido)-2-(trifluoromethyl)benzoate polystyrene (7)

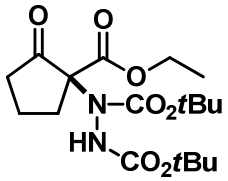
Azidomethylpolystyrene resin (0.60 g, *f* = 0.521 mmol g^{-1}) was swollen in 6 mL of DMF/THF (1:1) mixture for 10 minutes, then 4-ethynylbenzyl 4-(3-((1*R*,2*R*)-2-(piperidin-1-yl)cyclohexyl)thioureido)-2-(trifluoro-methyl)-benzoate **5** (0.40 mmol, 0.22 g) was added. Afterwards, CuI (0.08 mmol, 0.015 g) and DIPEA (1.56 mmol, 270 µL) were added to the reaction flask and the reaction mixture was heated at 40 ºC in an oil bath and shaken for 4 days. The reaction followed by IR spectroscopy, and after it was completed, the resin was filtered and washed with DMF (200 ml), H_2O (200 ml), THF (200 ml), MeOH (200 ml), and THF (200 ml) again. The resin was dried overnight in vacuo at 40 ºC.

IR (ATR): ν = 3025, 2925, 1735, 1600, 1539, 1492, 1285 cm^{-1}.

A 91% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N 3.13; found: C 84.50, H 7.69, N 3.13, S 0.65, Cu 0.04; *f* = 0.37 mmol g^{-1}.

General Reaction Conditions for the α-Amination Reaction

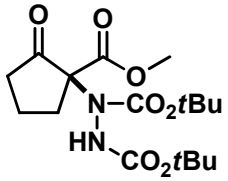
To a solution of PS-supported catalyst (2 mol%) in toluene (0.5 mL) was added the corresponding azodicarboxylate (0.2 mmol) and 1,3-dicarbonyl compound (0.3 mmol, 1.5 equiv.). The mixture was stirred at the reported temperature for each different substrate until TLC analysis showed that the limiting compound was completely consumed. The reaction mixture was directly purified by flash column chromatography to afford the desired product.



(*S*)-Di-*tert*-butyl 1-(1-(ethoxycarbonyl)-2-oxocyclopentyl)hydrazine-1,2-dicarboxylate (12)[23]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 92% yield and 93% ee.

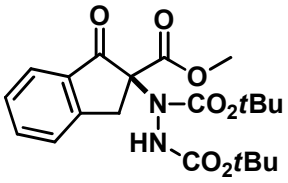
HPLC: AD-H column, hexane/*i*-PrOH (95:5), 1.0 mL·min^{-1}, 210 nm, t_R minor = 10.6 min, t_R major = 18.1 min.



(*S*)-Di-*tert*-butyl 1-(1-(methoxycarbonyl)-2-oxocyclopentyl)hydrazine-1,2-dicarboxylate[23]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 90% yield and 93% ee.

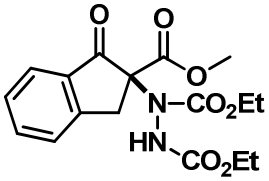
HPLC: IA column, hexane/EtOH (95:5), 1.0 mL·min^{-1}, 210 nm, t_R minor = 7.1 min, t_R major = 7.7 min.



(*S*)-Di-*tert*-butyl 1-(2-(methoxycarbonyl)-1-oxo-2,3-dihydro-1H-inden-2-yl)hydrazine -1,2-dicarboxylate[23]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 92% yield and 80% ee.

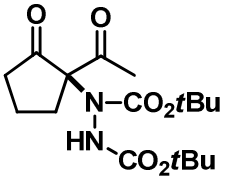
HPLC: AI column, hexane/*i*-PrOH (90:10), 1.0 mL·min^{-1}, 220 nm, t_R minor = 11.3 min, t_R major = 15.3 min.



(S)-Diethyl 1-(2-(methoxycarbonyl)-1-oxo-2,3-dihydro-1H-inden-2-yl)-hydrazine-1,2-dicarboxylate[20c]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 94% yield and 48% ee.

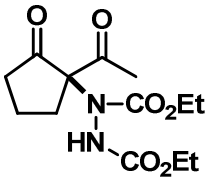
HPLC: IA column, hexane/*i*-PrOH (90:10), 1.0 mL·min^{-1}, 220 nm, t_R minor = 15.8 min, t_R major = 25.8 min.



(*R*)-Di-*tert*-butyl 1-(1-acetyl-2-oxocyclopentyl)hydrazine-1,2-dicarboxylate[23]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 91% yield and 72% ee.

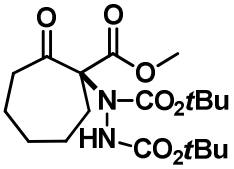
HPLC: AD-H column, hexane/*i*-PrOH (90:10), 1.0 mL·min^{-1}, 210 nm, t_R minor = 5.8 min, t_R major = 7.4 min.



(*R*)-Diethyl 1-(1-acetyl-2-oxocyclopentyl)hydrazine-1,2-dicarboxylate[23]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 93% yield and 66% ee.

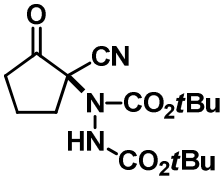
HPLC: OD-H column, hexane/EtOH (95:5), 1.0 mL·min^{-1}, 210 nm, t_R major = 11.8 min, t_R minor = 12.9 min.



(*S*)-Di-*tert*-butyl 1-(1-(methoxycarbonyl)-2-oxocycloheptyl)hydrazine-1,2-dicarboxylate[23]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 71% yield and 80% ee.

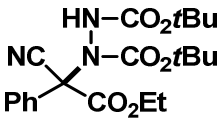
HPLC: OD-H column, hexane/*i*-PrOH (97:3), 1.0 mL·min^{-1}, 210 nm, t_R major = 11.8 min, t_R minor = 12.9 min.



(*R*)-Di-*tert*-butyl 1-(1-cyano-2-oxocyclopentyl)hydrazine-1,2-dicarboxylate[23]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 37% yield and 25% ee.

HPLC: IA column, hexane/*i*-PrOH (90:10), 1.0 mL·min^{-1}, 220 nm, t_R major = 6.8 min, t_R minor = 8.6 min.



(*S*)-Di-*tert*-butyl 1-(1-cyano-2-ethoxy-2-oxo-1-phenylethyl)hydrazine-1,2-dicarboxylate[20b]

Following the general procedure for the α-amination reaction as described above the title compound was obtained in 89% yield and 10% ee.

HPLC: AD-H column, hexane/*i*-PrOH (70:30), 1.0 mL·min^{-1}, 254 nm, t_R minor = 6.6 min, t_R major = 15.9 min.

CONCLUSION AND OUTLOOK

CONCLUSION AND OUTLOOK

The use of solid supported organocatalysts obtained via covalent immobilization has a great potential for versatile transformations. Besides, the immobilized catalysts, which show high catalytic activity and selectivity relative to their homogeneous counterparts, have additional advantages like easy work-up, recovery and reuse of the expensive species, and the possibility of continuous flow applications. The main goal of this thesis was to achieve the synthesis of polystyrene supported organocatalysts and to use them in different asymmetric transformations. The catalysts synthesized in this thesis are summarized in figure 5.1.

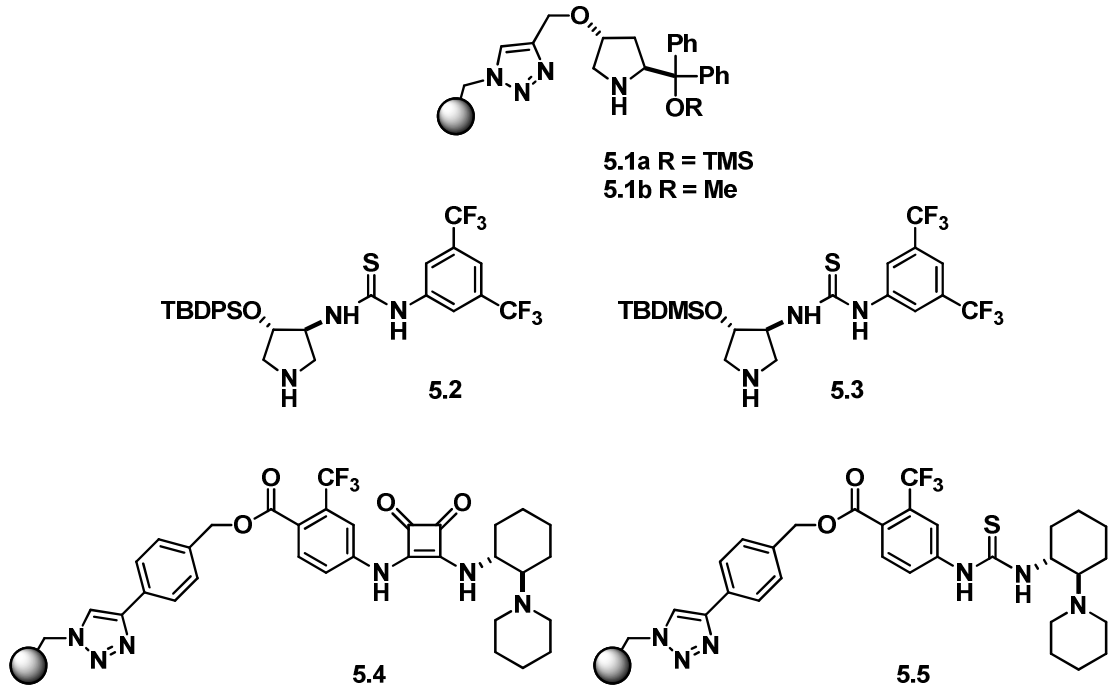


Figure 5.1. Homogeneous and heterogeneous catalysts synthesized in the present work.

Following the general approach implemented by our group, PS-supported organocatalysts were obtained by CuAAC reaction, which gives significant improvement over previously existing supporting methodologies in terms of reaction control, high functionalization and orthogonal chemistry to introduce the ligands. The immobilized catalysts have been evaluated in asymmetric carbon-carbon, and carbon-nitrogen bond forming reactions by using different organocatalytic activation pathways.

In **Chapter II**, α,α-Diphenylprolinol trimethylsilyl- **5.1a** and methyl **5.1b** ethers have been anchored onto a polystyrene resin and they have been used in the asymmetric addition of malonates and nitromethane to α,β-unsaturated aldehydes. The reactions are taking place via iminium intermediates, and catalyst **5.1a** was found to mediate the addition of dialkylmalonates and nitromethane to α,β-unsaturated aldehydes more efficiently than **5.1b**. The ultimate goal of the preparation of catalysts **5.1b** was to obtain a more robust catalyst, lacking the desilylation problem. However, immobilized α,α-diphenylprolinol methyl ether catalyst **5.1b** did not give the expected catalytic activity.

In **Chapter III**, the preparation of pyrrolidine-based thiourea organocatalysts has been described with their evaluation in *anti*-Mannich reactions. The impact of the substitution pattern on the catalytic activity and selectivity has been shown. The reaction of *N*-*p*-methoxyphenyl protected α-iminoglyoxylate with different aldehydes and ketones catalyzed by **5.2** and **5.3** gave good yields and moderate enantio- and diastereoselectivities. The reason of the moderate selectivity might be resulting from the positions where the catalyst backbone was functionalized, which may not be in the proper array for a selective reaction.

In **Chapter IV**, the PS-supported squaramide organocatalyst **5.4** has been prepared in four steps and it has been evaluated in the enantioselective Michael addition reaction of 1,3-dicarbonyl compounds to β-nitrostyrenes under batch conditions. The supported squaramide catalyst **5.4** has shown a catalytic performance comparable to its homogeneous counterpart and additionally, catalyst **5.4** could be recycled up to 10 times without significant loss in the catalytic activity. The efficiency of the catalyst has been highlighted by implementation of the continuous flow Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes, which was done with very low catalyst loadings and gave remarkable activity and selectivity even after long time use.

At the same time, the PS-supported thiourea organocatalyst **5.5** was prepared with an approach adapted from the synthesis of squaramide organocatalyst **5.5**. This thiourea was used in the α-amination reaction together with catalyst **5.4**, good to moderate results being obtained in the α-hydrazination of 1,3-dicarbonyl compounds. However, even if the synthesis of catalyst **5.5** could be reproduced following the initial attempt these batches showed much lower activity

and selectivity. After that, batches of PS-supported thiourea organocatalysts were prepared following alternative routes but giving the same disappointing results.

Overall, in the present thesis the advantages of solid supported catalysts have been demonstrated successfully in the recycling and continuous flow applications. Therefore, we have been able to develop effective polymer-supported organocatalysts with high catalytic activities and enantioselectivities and with robustness being their main feature.